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International Medical Digest

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General Medicine

The Effects of Magnesium upon Cardiac Arrhythmias — ENSELBERG, CHARLES D., SIMMONS, HENRY G. AND MINTZ, ARTHUR A.—*American Heart Journal*, 39: 703 (May) 1950.

"This study was undertaken in order to reexamine the influence of magnesium upon various arrhythmias, chiefly those associated with digitalis administration and including definite digitalis intoxication. Altogether 25 patients were studied, of whom only 1 had no demonstrable heart disease. The others had arteriosclerotic, hypertensive, or rheumatic heart disease, and were in mild to moderate degrees of decompensation. Their rhythmic mechanisms were as follows: ventricular extrasystoles, 14 (sinus rhythm, 6; auricular fibrillation, 8; with digitalis intoxication, 10; no digitalis given, 4); incomplete heart block (prolonged auriculoventricular conduction from digitalis intoxication), 1; complete heart block (no digitalis), 1; sinus arrest (digitalis intoxication), 2; auricular flutter without extrasystoles (digitalis but no toxicity), 2; and auricular fibrillation without extrasystoles (digitalis but no toxicity), 5."

"Magnesium sulfate was given intravenously in 20 per cent solution. All patients received 20 cc. of the salt, the injection being made as rapidly as possible. The injection usually was completed in 4 to 10 seconds, the beginning and end being indicated on the electrocardiogram. Continuous electrocardiographic recording was made for the first minute or two after the start of injection, and further records at short intervals thereafter whenever visual observation of the string shadow indicated a change in rate or rhythm. When ventricular extrasystoles were present their frequency was expressed as a fraction indicating the number of extrasystoles among the total number of ventricular beats counted. Since short strips often show variation in the frequency of extrasystoles every effort was made to count at least 100 consecutive beats in order to obtain a truer value of their occurrence."

"Twenty-nine injections of magnesium sulfate were given to 25 patients. In each case there was a subjective sensation of heat in the upper parts of the body and in most cases there was visible reddening of the blush areas. These changes appeared within a few seconds of the end of the injection, and were occasionally quite unpleasant to the patients. However, there was little apprehension, since all patients had been forewarned and expected the reaction. On 1 occasion, after about 6 cc. had been injected there was accidental extravenous infiltration of about 5 cc. The infiltration proved to be innocuous both subjectively and objectively. Sometimes during the course of injection, but usually a few seconds after it, the electrocardiogram showed numerous continuous artifacts. These rarely lasted for more than 30 seconds, and were often too minor to mar the record. They appeared usually as sharp, frequent oscillations in the base line and T wave.

"1. Ventricular Extrasystoles.—Sixteen trials were made in 14 cases." There was a striking diminution or abolition of extrasystoles in every instance but 1. This occurred within four minutes, and often in less than one or two minutes after the end of injection. "Almost always the effect wore off in a few minutes, and lasted as long as 30 minutes in only 1 case. Often either before or after the reduction in extrasystoles, magnesium caused a transient increase in their frequency, and occasionally extrasystoles from new foci appeared for a few seconds. On 1 occasion a bout of bidirectional ventricular tachycardia lasting six seconds appeared just before the magnesium effect was dissipated. Extrasystoles were not provoked in any patient in this series in whom they had been absent prior to administration of magnesium.

"2. Incomplete Heart Block.—In 1 patient, the P-R interval was shortened from 0.29 to 0.27 second as the rate increased from 90 to 120 in one minute. There was no further change for five minutes, when Wenckebach periods appeared with P-R intervals up to 0.39 second. In six minutes the effect was gone.

"3. Complete Heart Block.—In 1 patient with a ventricular rate of 20, the only change found was a transient sinus tachycardia with unaltered ventricular rate. The effects wore off within eight minutes.

"4. Sinus Arrest.—Two patients exhibiting this arrhythmia showed similar responses." One case received magnesium sulfate on three occasions, a week apart, while her digitalis was being continued. "Each time the mechanism of sinus arrest was abolished within 30 seconds, and replaced by sinus tachycardia. The effects endured for 20 minutes, 4 minutes, and 3 minutes. There was sudden inversion of the T wave and shortening of the P-R interval during the tachycardia."

One case had sinus arrests every 3 to 10 beats, followed by sinus and auriculoventricular nodal escapes. "In one-half minute after magnesium sulfate, the sinus arrests disappeared and the heart rate increased slightly. In three minutes the sinus arrests reappeared and the P-R interval increased to 0.28 second. For the next two minutes the arrests were more frequent and the escapes from arrest were all by the auriculoventricular node. In 15 minutes the effect was completely dissipated.

"5. Auricular Flutter.—In 2 patients with auricular flutter, both on digitalis, the magnesium effects were contradictory. The ventricular rate increased in 1 and fell in the other. In the latter patient the fall in rate was due to transient increase of auriculoventricular block from 2: 1 to 4:1.

"6. Auricular Fibrillation.—Of 5 patients on digitalis without premature beats, sharp effects occurred in 2. These showed slowing of the ventricular rate, from 88 to 50 in 1 patient, and from 66 to 20 in the other. The action appeared in each instance within one-half minute and wore off in four and two minutes, respectively.

"7. Auriculoventricular Conduction.—In normal sinus rhythm, with or without premature beats, alterations of the P-R segment were neither striking nor uniform. Within the first minute or two there was usually slight shortening of the P-R interval, and after two minutes there was, occasionally, some lengthening." The largest change was in 1 case where the P-R interval increased from 0.16 to 0.20 second in two minutes.

"8. T Wave.—This deflection was usually made more negative in leads I or II by magnesium, though the magnitude of this change was rarely great. This, like other magnesium effects, was of short duration.

"9. Rate.—Almost always, regardless of the rhythm, the initial result was a slight to moderate increase in auricular rate when a sinus mechanism was present, and in ventricular rate during auricular fibrillation. Usually before the effect was dissipated the rate became somewhat slower than the control. The greatest increase was in a case of sinus arrest where the rate rose on one occasion from 60 to 112, and the greatest decrease was in a case of auricular fibrillation, mentioned above, where the ventricular rate suddenly fell to 20."

"It is concluded that the therapeutic use of magnesium in arrhythmias is limited by its ephemeral action and by its occasional undesirable effects."

Long Term Follow-Up Study of Penicillin-Treated Subacute Bacterial Endocarditis — GORLIN, RICHARD FAVOUR, CUTTING B. AND EMERY, F. JEAN — *New England Journal of Medicine*, 242: 995 (June 29) 1950.

"From 1944 through 1947, a period arbitrarily chosen to provide at least a one year follow-up study on the most recent cases, 60 patients with proved subacute bacterial endocarditis were admitted to this hospital. Diagnosis was substantiated by two positive blood cultures, the association of two or more classic clinical signs with at least one positive blood culture, or postmortem examination. Patients were selected for study who had received 200,000 units or more of penicillin a day for at least 10 days and who either were followed for over a year after therapy or came to autopsy. Thirty-eight patients met these criteria, and the remaining 22 were excluded from further analysis."

"Two of the 38 patients were retreated for reinfection, 15 and 16 months, respectively, after bacteriologic cure of the initial infection. During the interim, both were followed in this clinic, where they were noted to be free of the stigmas of the smoldering or 'bacteria free' stage of bacterial endocarditis. Thus 40 episodes of treated subacute bacterial endocarditis in 38 patients were analyzed in this study."

"The average age at onset for the group was 34 years. Twenty were females, and 18 males. Eighty-three per cent had preexisting rheumatic valvular disease. Among the congenital defects present in 6 patients, there were 5 cases of patent ductus arteriosus, 1 of interventricular septal defect and 1 of a bicuspid aortic valve. Dental extractions or major fillings without associated penicillin prophylaxis had been carried out in 38 per cent of the patients within the immediate weeks before the development of endocarditis. Upper respiratory infections, furunculosis, pyelitis, appendicitis and cystitis preceded endocarditis in 6 other cases, whereas in 20 no antecedent infection could be implicated. The alpha-hemolytic streptococcus was the responsible organism in 33 of the 40 treated episodes. There were 2 double infections; an infection due to *Alcaligenes faecalis* developed in 1 patient during penicillin treatment for an endocarditis caused by alpha-hemolytic streptococcus; the other patient had endocarditis due to both alpha-hemolytic streptococcus and *Escherichia coli*. These organisms were isolated both from the blood during life and from the heart valves at autopsy in each of these patients."

"The average duration of infection, as indicated by onset of symptoms before admission, was three and a half months, with a range extending from two days to one year. Symptoms of infection were noted by all but 1 patient. Ninety-three per cent had a history of a murmur before infection developed, and in all the murmur remained essentially unchanged during the hospital stay. Sixty-four per cent of the patients who subsequently survived had a fever on admission, and all but 1 of those in the fatal cases were febrile at that time. Nine of the 12 patients who died had symptoms of congestive failure before the start of treatment, whereas such symptoms were present in only 3 of the 28 who recovered. Arthralgia, splenomegaly and embolic phenomena were slightly more common among the fatal cases. The presence of albumin in the urine, with red cells and casts in the sediment, was more common among those who subsequently did not survive.

"Fourteen patients were tested intracutaneously, before and after treatment, with a protein derived from beta-hemolytic streptococci. All had negative tests before therapy. Nine patients who subsequently survived, and 3 others, who at autopsy showed no evidence of active infection, had a positive test after therapy. Two patients, however, whose tests remained negative after therapy did show actively infected valves at autopsy.

"One patient, who relapsed three times before she was finally cured, showed a positive skin test shortly after each course of treatment. The test subsequently reverted to negative on three occasions, each time preceding bacteriologic and clinical relapse. After final recovery the skin test remained positive over a four year period until death from congestive failure.

"To some extent weight loss and the degree of anemia depended upon duration of infection before admission; a corollary of this finding was the absence of anemia in 25 per cent of the patients before the start of treatment. Although the erythrocyte sedimentation rate was elevated in most patients on admission, the rate did not always fall with successful treatment."

"When this series was first begun in 1944, penicillin was scarce, and optimal doses were unknown. At that time, therapy consisted of 200,000 units of penicillin given intravenously for 14 days. Duration of treatment was soon extended to three and then five weeks or longer, depending on the clinical response. At present, 2,000,000 units or more is given daily in divided doses intramuscularly every three hours, with the use of combined sodium and procaine penicillin in the latter weeks of therapy. Cure has resulted from as little as 200,000 units daily for two weeks or as much as 4,000,000 units daily for six weeks, but no one treatment schedule has been uniformly successful. Four patients with persistent fever and bacteremia received in stepwise fashion increased amounts of penicillin. Three of them re-

sponded satisfactorily within two to four days to the change in treatment. Despite changing therapeutic practices, a relatively stable year to year penicillin cure rate has been observed, with an over-all result of 28 cures in 40 episodes, or 70 per cent. That only the patients with the more refractory cases of subacute bacterial endocarditis were sent to the hospital in the last few years may explain the paradox of a stable annual cure rate in the face of increased treatment schedules.

"Twenty-six of 28 cured patients showed a fall in temperature and pulse rate within 48 hours after the start of treatment, and both temperature and pulse fell to normal within 5 to 10 days. In contrast, 11 of 12 patients subsequently dying of the disease showed no fall in temperature with treatment. Other clinical and laboratory evidences of healing were slower to appear. Encouraging signs, however, were clearing of the urinary sediment, disappearance of the anemia, return of the sedimentation rate to normal and disappearance of splenomegaly."

"Gram-negative bacilli were present along with the alpha-hemolytic streptococcus in 2 patients, neither of whom responded to available therapy, and both subsequently died. In this series no other organisms were found to be insensitive to penicillin in vitro."

"Congestive failure occurred in 38 per cent of this group at some time. Failure developed in 13 during the course of the untreated disease, and despite therapy, 77 per cent of these patients subsequently died. Failure appearing for the first time in the immediate post-treatment period occurred in only 2 persons. The onset of failure in these 15 patients was not related to duration of infection before admission.

"Findings at autopsy on patients dying with congestive failure in this disease indicated that the failure was due to new lesions of the myocardium as well as to valvular changes. In this small group of 13 patients who died during or shortly after therapy, the presence of failure in 10 was associated with diffuse myocardial damage in 8. Marked valvular damage was not always associated with failure, and in some cases failure was present despite remarkably well healed valves. There were 2 examples of single lesions as the cause for failure: A patient with subacute bacterial endocarditis of the right ventricular endocardium alone had a diffuse myocarditis, and another with a normal myocardium had gross destruction of both aortic and pulmonic valves. Rheumatic myocarditis was seen in only 3 of the 13 autopsied cases. Failure was present in 2 of these, despite the absence of striking valvular damage.

"Organisms highly susceptible to penicillin in vitro were found in the hearts of 8 of the 12 patients who died of the disease and in 7 of the 10 who died with congestive failure, although all had received two to four weeks of penicillin therapy."

"Four patients (10 per cent) had definite evidence of renal lesions; 3 had focal embolic glomerulonephritis at autopsy, and the other is living. Three of the 4 had clinical signs of renal insufficiency. One patient died of combined uremia and congestive failure; another, in whom urinary signs of a renal lesion developed in the course of the infection, has had microscopic hematuria during the two years since that time. All 4 had had subacute bacterial endocarditis for over two months before therapy, and 3 showed a good bacteriologic response to treatment."

"Four patients (10 per cent) had clinical or autopsy evidence of major pulmonary embolism. All died, 2 of the consequences of repeated embolism, and 2 of cardiac failure. All had right-sided lesions of the heart, 3 being subacute bacterial endocarditis, and the other an auricular mural thrombus."

"Splenic infarcts were commonly demonstrated both by clinical signs and by pathological examination. Only 1 patient had a serious complication therefrom: Death resulted from rupture of an infarct, with massive hemoperitoneum, 120 days after initial treatment of subacute bacterial endocarditis, during a clinical and bacteriologic relapse."

"Clinically noticeable cerebral embolization occurred in 4 cases (10 per cent). One patient died of repeated cortical infarcts and terminal hyperpyrexia. Two others suffered subarachnoid hemorrhages, but recovered satisfactorily. A fourth had several severe bilateral middle-cerebral-artery emboli, with residual hemiplegia."

"In 1 patient an ulnar-artery aneurysm developed prior to treatment. Another had multiple subcutaneous abscesses from which the alpha-hemolytic streptococcus was isolated."

"Of the 38 patients in this study, 27 remained bacteriologically cured for more than a year. Nine of these were followed for four to six years, 12 for two to four years, and 6 for one to two years. Seven patients of this group died. A twenty-eighth patient, who was considered cured, died of a myocardial infarction due to coronary arteriosclerosis two weeks after treatment. Vegetations were found to be healed at autopsy. This patient was the only 1 who died during the first year following cure of infection. . . . Four patients died of congestive failure, 2 of recurrent subacute bacterial endocarditis, and another of an unrelated late postoperative complication.

"Although 7 of the patients who recovered had some cardiac, renal or neurologic disability due to the infection, only 1 was believed to have died from such a disability." In 3 of the 5 patients who showed cardiac decompensation in the period after treatment failure first developed during the course of infection.

"Follow-up x-ray examinations of the heart were made in 16 of the patients who recovered. Six showed an increase in heart size since the time of infection; 8 showed no change; and 2 actually were observed to decrease in size. Major increases in heart size were associated with congestive failure in only 3 cases.

"Cardiac murmurs that were different from those heard during the infection were observed in 9 of the 27 patients at follow-up examination. Four of the murmurs showed a gradually increasing intensity dating from the time of the endocarditis, whereas the other 5 were considered unrelated and due to progression of the rheumatic heart disease.

"None of the patients had anemia. The sedimentation rate was elevated in 5 patients without known cause. Two patients, 1 with nephritis and the other with congestive failure, had abnormal urinary sediments; none had diminished renal function. In all but 1 case the streptococcus skin test was positive."

Intravenous Administration of Paraamino Salicylic Acid for Streptomycin-Resistant Tuberculosis of the Trachea. Report of a Case — CARR, DAVID T., SEYBOLD, WILLIAM D., SCHMIDT, HERBERT W. AND KARLSON, ALFRED G. — *Minnesota Medicine*, 33: 363 (April) 1950.

"Paraamino salicylic acid (PAS) is a new antituberculosis drug which is effective against both streptomycin-sensitive and streptomycin-resistant tubercle bacilli. The following report of a case illustrates the efficacy of the new drug against tuberculosis due to streptomycin-resistant tubercle bacilli. It is of particular interest as most of the PAS was given intravenously to avoid the gastrointestinal irritation which usually develops when this drug is given orally.

"Report of Case.—A white woman, 32 years of age, registered at the Mayo Clinic on January 24, 1949. A diagnosis of tuberculosis of the left lung had been made in January, 1948. She had entered a hospital where she rested in bed and also underwent therapeutic pneumothorax on the left side. In spite of this, tuberculosis of the left main bronchus and of the larynx had developed for which she was given streptomycin, one course of 1 Gm. daily for 55 days and another of 1.5 Gm. daily for 123 days. The laryngeal lesion healed but the bronchial lesion persisted, producing stenosis of the left main bronchus. In addition, tubercles developed in the left side of the lower end of the trachea. Stained smears of the sputum remained positive for acid-fast bacilli throughout the period of treatment. Diagnostic study at the clinic revealed extensive disease of the left lung, stained smears of sputum being positive for acid-fast bacilli. Bronchoscopic examination revealed ulceration on the left side of the lower 3 inches (7.6 cm.) of the trachea. The lumen of the left main bronchus was stenosed to a pinpoint opening so that the depth of this bronchus could not be examined. The right main bronchus appeared normal.

"In spite of tracheal disease and the probability that the tubercle bacilli were highly resistant to streptomycin, pneumonectomy on the left was advised. This was performed on February 1, 1949, and at the same time partial thoracoplasty was done,

parts of the fifth, sixth and seventh ribs being removed. The immediate postoperative course was satisfactory and on February 17, 1949, a second stage thoracoplasty was performed, parts of the second, third and fourth ribs being removed. During this time she was given 1 Gm. of dihydrostreptomycin each day even though it seemed probable that tubercle bacilli were resistant to this drug.

"On February 22, 1949, bronchoscopic examination revealed persistence of the extensive ulceration in the lower end of the trachea, and stained smears of sputum were still positive for acid-fast bacilli. By this time it had been determined that the tubercle bacilli were resistant to streptomycin, the microorganism growing in culture medium containing 100 micrograms of streptomycin per ml. of medium.

"Treatment with large doses of PAS was advised and to avoid the gastrointestinal irritation which this drug causes, the sodium salt of PAS (NaPAS) was administered intravenously. On February 26, 1949, 4 Gm. of NaPAS was given and the daily dose gradually increased until 30 Gm. was being given each day. The total daily dose was added to 1,000 cc. of 5 per cent glucose in distilled water and injected over a period of about eight hours. During the third month of treatment only 10 Gm. of NaPAS was given intravenously each day due to an inadequate supply of the drug. This was supplemented by 14.4 Gm. of PAS administered orally each day in three equal doses. The total dose of PAS during the three months of treatment was 1,646 Gm. of NaPAS given intravenously and 452.7 Gm. of PAS by the oral route.

"There was a dramatic response to this treatment. On March 23, 1949, a bronchoscopic examination revealed marked healing of the lesion in the trachea with only a small ulcerated area remaining just above the orifice of the stump of the left main bronchus. The ulceration extended down into this stump and was covered with a grayish white exudate. Stained smears of sputum which had been positive persistently for acid-fast bacilli during the first month after pneumonectomy were now negative. However, cultures of sputum at this time proved to be positive for acid-fast bacilli.

"After two months of treatment with PAS, a bronchoscopic examination revealed complete healing of the tracheal ulceration. The orifice of the left main bronchus was slightly inflamed and bled a little when touched with forceps. A cultured specimen of the bronchial secretions obtained at this time did not show acid-fast bacilli to be present. After the third month of treatment had been completed, bronchoscopic examination did not reveal evidence of tuberculosis. The orifice of the left main bronchus appeared as a small dimple in the lateral wall of the lower portion of the trachea. The mucosa appeared normal but bled on bronchoscopic manipulation. Six specimens of sputum, gastric washings and bronchial secretion were cultured. Negative results were obtained from five cultures but one culture of sputum yielded a few colonies of acid-fast bacilli. During the three months of treatment the roentgenographic appearance of the right lung remained unchanged. At this stage of the treatment the patient left the hospital to continue rest in bed at home.

"She returned to the clinic on August 22, 1949, for reexamination, having had no symptoms during the interval. A roentgenogram of the chest did not show any change when compared with the film made in May, 1949. A bronchoscopic examination revealed no evidence of active disease. The stump of the left main bronchus still appeared as a small dimple on the left in the lower portion of the tracheal wall. The mucosa appeared normal and did not bleed on manipulation. No secretions were present. Bronchial washings were obtained for culture for acid-fast bacilli. Two specimens of gastric washings also were cultured. One of the gastric specimens yielded a few colonies of acid-fast bacilli but the results of the other two cultures were negative.

"Evidence of toxicity to PAS was searched for carefully during and after the period of treatment but none was found. There was no sign or symptom of gastrointestinal irritation even when 30 Gm. of NaPAS was given intravenously each day. The results of weekly blood counts, determinations of hemoglobin and urinalyses remained within normal ranges. Biweekly to monthly tests of renal and hepatic function showed no evidence of damage to the

Table I. Concentration of PAS in Blood Serum at Intervals During a Period of 24 Hours*

Hours after beginning injection	Concentration of PAS in blood serum (milligrams per 100 cc.)	
	Free PAS	Total PAS
4¼	32.0	28.6
11	4.9	6.4
24	<1.0	<1.0

*In the first seven and a third hours the patient was given 30 Gm. of NaPAS intravenously.

Table II. Excretion of PAS in the Urine During a Period of 24 Hours*

Period of eight hours	Volume of urine, cc.	PAS, Gm.	
		Free	Total
First	1,100	17.0	16.6
Second	1,100	7.0	8.0
Third	200	1.5	3.4
Totals		25.5	28.0

*In the first seven and a third hours the patient was given 30 Gm. of NaPAS intravenously.

kidneys or liver. The prothrombin time varied from 19 to 23 seconds. There was some irritation of the veins with thromboses but it was possible to give the intravenous injection every day for 90 consecutive days.

"The concentration of PAS in the blood serum and the excretion of PAS in the urine were studied during a period of 24 hours in which the patient was given 30 Gm. of NaPAS intravenously during the first seven and a third hours. The results are given in tables I and II.

"A streptomycin sensitivity test was performed on each of the positive cultures for acid-fast bacilli. The microorganisms remained resistant to streptomycin throughout the period of observation. Sensitivity to PAS was also determined for all of the positive cultures. There was no evidence of increase in resistance to PAS, all of the cultures being sensitive to between 0.0045 and 0.072 mg. of PAS per 100 ml. of culture medium.

"Reexamination of the patient in December, 1949, revealed no evidence of active tuberculosis. Culture of 3 specimens of gastric washings and one specimen of bronchial secretions aspirated during bronchoscopy did not produce acid-fast bacilli."

"It is worthy of note that a similar preparation of NaPAS was administered to 2 other patients by the intravenous route and in both cases acute hemolytic anemia developed after a few days of treatment. The preparation had been stored at room temperature for several months and analysis revealed that 24 per cent of the NaPAS had decomposed to meta-aminophenol and related compounds. For this reason it would seem wise to use only a freshly prepared solution of NaPAS for parenteral administration."

Capillary Fragility Studies in Diabetes Mellitus and the Use of Rutin in Diabetic Retinitis — BARNES, ROBERT H. — *American Journal of the Medical Sciences*, 219: 368 (April) 1950.

It is the purpose of this paper to present the results of studies on the strength of capillaries in diabetes mellitus and to note the effect of rutin therapy on increased capillary fragility and diabetic retinitis.

"In the present study the Göthlin technique was not used because of the time involved in doing the test. Methods in which the pressure is maintained midway between systolic and diastolic levels were not used because of pain frequently caused by the higher pressure and because of the possibility of producing a vascular thrombosis. A technique was standardized on a group of 50 nonhypertensive, nondiabetic persons, both male and female ranging in age from 18 to 76 years (average 44.6 years)." This group was made up of patients who had no evidence of nutritional deficiency, blood dyscrasia, hypertension or diabetes. "The following technique was used: A blood pressure cuff was applied to the upper arm and pressure maintained at 80 mm. of mercury for four minutes. The petechiae were counted in a 6 cm. circle on the flexor surface of the forearm in an area in which there seemed to be the most petechiae. The petechiae were counted, using a hand lens and a bright light. Other authors have used a definite area on the forearm mapped out prior

to applying the pressure." In these cases the circle was drawn in the area which contained the most petechiae regardless of its location on the surface of the forearm. "It was observed repeatedly that often there would be few or no petechiae just below the antecubital fossa and at the same time there might be many at the wrist or vice versa. In this control group 42 showed a petechial count between 0 and 10, while 5 had a count between 10 and 20; in only 3 cases was the count over 20. From this control group, therefore, it was concluded that with this method a count of over 20 petechiae was definitely abnormal."

The authors studied 220 patients. "The following data were recorded on each patient: age at onset of diabetes, present age, duration of diabetes, weight, insulin dose, blood pressure, results of funduscopic examination and capillary fragility. From these data patients were divided into 4 main groups: 1, those with diabetic retinitis and increased capillary fragility; 2, those with retinitis and normal capillary fragility; 3, those without retinitis but with increased capillary fragility; and 4, those with no retinitis and normal capillary fragility. These 4 groups were also classified as to whether or not hypertension was present. The patient was regarded as having hypertension if the systolic pressure was over 150 mm. or the diastolic over 90 mm. of mercury. In 38 of the 220 patients observations were made on the effect of rutin on capillary fragility and retinitis."

Of the 220 patients examined, 68 had both diabetic retinitis and abnormal capillary fragility; 12 had retinitis with normal fragility. "Thus, 85 per cent of the 80 patients with retinitis had increased capillary fragility. Of the remaining 140 patients, 68 had abnormal capillary fragility but no retinitis and 72 had both normal retinas and capillaries. Thus 48.5 per cent of the patients without retinal pathology showed abnormally weak capillaries indicating that diabetes per se is associated with increased capillary fragility." That hypertension contributed to the high incidence of both retinitis and increased capillary fragility in these cases is shown by the fact that it is associated twice as frequently with retinitis and increased capillary fragility as with normal retinas and capillaries, 66.1 per cent, as contrasted with 33.3 per cent. As a corollary to this, of the 103 patients with hypertension it was noted that 49 had retinitis; whereas, of the 117 cases without hypertension only 31 cases had retinitis. The average duration of the diabetes in the group with retinitis and increased capillary fragility was 17.2 years. "In marked contrast, in the group with no retinitis and normal fragility the average duration was 10.5 years. There is very little difference in the average age of the different groups. The patients with retinitis and increased capillary fragility had the largest percentage of long duration juvenile diabetics.

"Of the 80 cases with diabetic retinitis 32 were treated with rutin for a period varying from 6 weeks to 30 months with an average of 12 months. Ten patients were treated for 18 months or longer with a maximum of 30 months. An additional 6 patients without retinitis but with increased capillary fragility were also treated in an attempt to correct the fragility and thus possibly prevent retinitis. Tests of capillary fragility were done 147 times on the 38 patients. The average age of the 32 patients with retinitis was 43.3 years with an average duration of the diabetes of 19 years. Fourteen of these were patients with onset of diabetes in childhood, the majority of whom had severe retinitis proliferans, hypertension, albuminuria and peripheral arteriosclerosis. The average duration of the disease among the juveniles was 20.1 years; the shortest duration in this group was 13 years and the longest 26 years. The majority of the 32 patients with retinitis were followed both by the internist and the ophthalmologist. Hypertension was present in 53.1 per cent. Most patients received 180 mg. of rutin a day although 10 took 300 mg. or more per day. One patient took a maximum daily dose of 1,320 mg. The behavior of the capillary fragility during the period of rutin therapy was as follows: decreased to normal, 4; decreased but not to normal, 4; remained approximately the same, 13; increased, 6; fluctuated, 5. . . . Among the 10 patients treated with rutin for 18 months or longer, in 2 the capillary fragility returned to normal, in 1 it decreased, in 1 increased, in 4 remained approximate-

ly the same, and 2 fluctuated. Thus, in only 3 of 10 cases was the capillary fragility favorably affected despite the long duration of treatment. Among the 10 patients whose dosage of rutin was increased to 300 mg. or more of rutin per day none returned to normal levels, 3 were decreased, 6 remained the same, and 2 fluctuated.

"The average age of the 6 patients treated with rutin who did not have retinitis but who did have increased capillary fragility was 32 years and they had had diabetes for an average of 15.1 years. They were treated over a period varying from 4 to 12 months with an average of 7.3 months. Only 1 patient of the 6 had hypertension. In 4 of the 6 the capillary fragility returned to normal while on rutin therapy, whereas in only 1 did it increase and in 1 it remained the same."

"Five of the 32 patients with diabetic retinitis while on rutin therapy had vitreous hemorrhages severe enough to impair vision. Three of these were taking 300 mg. of rutin or more daily while the other 2 were taking 180 mg. daily. It is significant that at the time of the hemorrhage 2 of these patients had a normal capillary fragility." A 33 year old female with diabetes of 15 years duration had typical diabetic retinitis. "She had been taking rutin orally for 13 months and her original capillary fragility test showed a petechial index of 50 by the Göthlin technique. She took 180 mg. of rutin daily from June 1948 to July 1949. . . . The capillary fragility was reduced from a high of 250 petechiae in December 1948 to a low of 20 petechiae on April 30, 1949. On June 19, 1949, while her capillary fragility was still relatively low she had a massive vitreous hemorrhage in the left eye. The capillary fragility test done two days later showed far too many petechiae to count in the 6 cm. circle. During the next month following the hemorrhage the patient took 25 mg. of rutin subcutaneously in addition to the 180 mg. orally. At the end of the month the capillary fragility had returned to normal with a petechial count of 10 and there was subjective improvement in vision. This case illustrates that rutin therapy may not prevent retinal hemorrhages even though the capillary fragility returns to a relatively normal limit. However, it must be emphasized that in this case in addition to the diabetic retinitis the patient had massive albuminuria, peripheral edema, hypertension and hypoproteinemia." A 49 year old female had had diabetes for 24 years. "In 1946 an ophthalmologist reported only a few small punctate hemorrhages in each retina. She was started on rutin therapy and during 1948 and 1949 she received 300 mg. of rutin daily. Her capillary fragility was never affected by the rutin therapy, remaining at a high level between 200 and 400 petechiae. In March 1949, three years after the ophthalmologist had described early diabetic retinitis, he stated that the patient showed marked retinitis proliferans in spite of the fact that she had been on rutin therapy." In contrast to the above may be cited the experience of a 29 year old female with onset of diabetes at the age of 4 years. "In 1947 an ophthalmologist described retinitis proliferans. She was started on rutin, 120 mg. daily at that time. The dose was gradually increased to 400 mg. per day. During 19 months of treatment there was no progress in the retinitis observed by the ophthalmologist. The capillary fragility fluctuated between a high of 136 to a low of 12 petechiae."

"The place of rutin in the treatment of diabetic retinitis is still not conclusively established and a proper evaluation must await further study."

Typhoid Fever Treated with Chloromycetin — GLORIEUX, E. — *Ars Medici*, 5: 372 (May) 1950.

The patient, 17 years old, went with 40 other students for a trip to Spain and Portugal from August 19, to September 9, 1949.

On August 24, 1 of the students contracted typhoid fever, and on the next day all of the group received an injection of vaccine.

On September 24, the patient consulted the author for multiple infected wounds of the legs with lymphangitis of the left foot. He was given 900,000 units of penicillin in 3 days and he improved rapidly.

He was seen again on October 6, complaining of fatigue, depression and melancholia. The lassitude was extreme on October 10 and muscular and articular pains appeared. He did not have any fever but

his pulse was 115. On the next day, his temperature rose to 102.2° F. while his pulse decreased to 110. He was depressed and complained of frontal headache, sore throat, pain in the left knee and abdominal discomfort with constipation. He was given 6 Gm. of polysulfonamide and a laxative.

His temperature on October 12 was 103.6° F., pulse 105. There was ileocecal gurgling. The spleen and liver were not enlarged. His tongue was coated and his breath was fetid; he had not had any stool. The sulfonamide treatment was continued. He remained depressed on October 13 but was not prostrated. He complained of pain in the left shoulder. He had two fluid stools and there was discomfort in the right iliac fossa where the gurgling persisted. His temperature remained high. The sulfonamide was replaced by sodium salicylate.

The only change on October 14 was the disappearance of the pains in the knee and shoulder. It was suspected that he had typhoid or paratyphoid fever in spite of the long incubation period. A blood culture was made and an examination of the blood showed 5,700 leukocytes with neutrophils 60 per cent, eosinophils 1 per cent, lymphocytes 32 per cent and monocytes 7 per cent. These findings were suggestive and he was given chloromycetin immediately. The first dose was 1 Gm., the second dose 1 hour later, 1 Gm., the third dose 1 hour later, 1 Gm.; thus 3 Gm. were given in 2 hours. He was then given 25 cg. every 3 hours for 24 hours and 25 cg. every 4 hours for 4 days, a total of 12 Gm. in 5½ days.

The fever began to decrease at once and his temperature became normal on the fifth day while the pulse became normal. The depression and gurgling in the iliac fossa disappeared and the stools became regular and molded.

The blood culture confirmed the diagnosis of typhoid fever. The clinical course was perfect except for profuse perspiration when his fever decreased. He was discharged on October 28.

This spectacular result seemed to be demonstrative. The decrease of the fever at the same time that the chloromycetin was given could not be explained as a coincidence. It was not possible that this was a case of early spontaneous cure because the blood culture was strongly positive.

Examinations were made of 6,000 samples of soil from all over the world and several microorganisms were found which were worthy of further study. An Actinomyces was isolated which showed an antibiotic activity against various bacteria. Less than two months later, this antibiotic was isolated in a pure state and it was termed chloramphenicol as it contained a derivative of dichloracetic acid. Several were able to synthetize this new product. Both the synthetic and natural form have identical chemical, physical and therapeutic properties and neither is toxic.

Chloromycetin is a neutral white substance with a bitter taste. It crystallizes in needles or elongated plates. It is stable in a neutral or slightly acid solution and resists boiling in distilled water for more than five hours. It is only slightly soluble in water (0.25 per cent) but is very soluble in organic solvents, especially propyleneglycol (15 per cent).

Experiments in man have shown that it is rapidly and almost completely absorbed through the gastrointestinal tract. The maximum concentration in the blood is reached in 2 hours after a single oral dose; 24 hours later no trace can be found in the blood. The concentration in the blood is proportional to the dose administered.

Absorption also occurs through the intraperitoneal routes, intravenously, subcutaneously or intramuscularly. Intramuscular injections may cause a local reaction with induration, edema or necrosis, so it should not be used. It is absorbed by the bile and to a lesser degree by the cerebrospinal fluid.

Elimination occurs chiefly through the urine and is very rapid. It begins half an hour after oral administration and reaches its maximum 4 to 6 hours later. About 8 per cent is found in a pure state in the urine and from 80 to 92 per cent is excreted in 24 hours in the form of an amido compound, probably monoglucuronide. This rapid excretion explains the slight accumulation of the product in the blood, even after prolonged administration and the absence of toxicity even after large doses. Oral doses of 1 Gm. per Kg. of weight in animals have only produced a transitory depression and 1.5 Gm. per

Kg. were required to produce dyspnea. Experiments in man have shown that doses of 1 Gm. daily for 10 days did not cause any modifications of the blood or urine.

Chloromycetin has been found to be active against the agents of brucellosis, Rickettsia, the neurotropic virus of psittacosis, venereal lymphogranulomatosis, the virus of atypical pneumonia, gram-negative bacilli responsible for urinary infections such as *Bacillus coli*, *Bacillus proteus* and *Aerobacter aerogenes*, the typhoid and paratyphoid bacilli and the agents of various affections such as pertussis, recurrent fever and cholera.

The first clinical trials for the treatment of typhoid fever were carried out in Malaya on 18 cases of which 10 were treated and 8 were used as controls. Treatment was begun on the tenth day of the disease after blood cultures were found to be positive. The chloromycetin was given in an initial dose of 50 mg. per Kg. of weight (3 Gm. in adults) followed by 25 cg. repeated every 2 hours until the temperature had become normal and then every 3 or 4 hours for 5 days, the total dosage being 19.1 Gm. in 8 days. The average duration of the fever in the 10 cases treated was 3.5 days after the first dose and it was 26 days in the control cases. Two of the treated patients had a relapse which responded rapidly to a second treatment. Cultures showed that the relapses were not due to the development of resistant strains. Two of the patients had serious complications; 1 had an intestinal perforation and the other had a grave hemorrhage; both recovered. These 2 complications prove that chloromycetin is not capable of preventing the evolution of anatomic lesions produced before the institution of treatment and this shows the necessity of an early diagnosis and early treatment.

A patient was treated who entered the hospital on the second week of his infection. He had an intestinal perforation on the fourth day of treatment. The chloromycetin was then associated with penicillin and later with streptomycin. The patient was saved without an operation.

In the first case reported in England, on the eleventh day of typhoid fever, an initial dose of 4 Gm. was administered followed by doses of 25 cg. every 2 hours with a total dosage of 22.75 Gm. There was a sudden decrease of the fever in 24 hours with oscillations for 3 days while the general condition improved rapidly.

The results obtained in 22 cases have been published by one writer; 10 patients were treated and 12 served as controls. One of the patients in each group died. Of the remaining 9 patients treated, signs of improvement were noticed in 48 hours after 8 Gm. of chloromycetin, 7 were apyretic on the third day and 2 others had a normal temperature on the fourth and fifth day. The clinical symptoms improved even more rapidly. The effect on the headache was really dramatic.

Another has reported a case treated on the fourth day of the disease. The temperature became normal on the fourth day of treatment. A total dose of 20 Gm. was given.

One writer reported 33 cases of typhoid fever treated with chloromycetin in which 25 were cured rapidly, 4 had a relapse and 4 died. He noted that of the 12 patients who were treated before the tenth day, all recovered.

During the course of a large epidemic of typhoid fever at Palermo, a report was made on 50 of the most severely infected patients who were treated with chloromycetin. It seemed that the temperature decreased more rapidly in the patients who were treated late. In certain cases with pulmonary complications penicillin was also used. Relapses were only observed in patients who were allowed to rise less than 10 days after the decrease of the fever.

A report was made on the case of a student who contracted typhoid fever accidentally in a laboratory on March 3. He entered the hospital on March 22 after he had had fever, loss of appetite and headache for 7 days. After treatment with acetylsalicylic acid, penicillin and streptomycin and a blood transfusion had given no results, he was treated with chloromycetin in the usual manner and in 24 hours his temperature decreased from 105° F. to 102.2° F. where it remained for 24 hours and then became normal. However, sibilant rales in the left lung required treatment with 50,000 units of penicillin every 4 hours for 3 days.

Stress has been laid on the good results obtained by chloromycetin in typhoidal en-

cephalitis. All similar cases had previously resulted in death. Of the 8 cases treated, 1 died from intestinal perforation although streptomycin, penicillin and chloromycetin had been administered, but treatment was only begun on the twentieth day of the disease. One other patient required as much as 6 Gm. daily and did not recover until 60 Gm. had been given along with 7.5 Gm. of aureomycin. The necessity of early treatment with sufficient doses is stressed in cases of ordinary typhoid fever.

Of 2 cases of paratyphoid fever reported, 1 patient recovered after 8 Gm. The other ceased treatment after 6 Gm. on account of the high cost of the drug. There was a relapse a month later but it was controlled by an initial dose of 3 Gm. followed by 1.5 Gm. daily for 5 days.

One writer has successfully treated 7 of 8 grave cases of paratyphoid fever and others treated 4 cases of typhoid fever in which the temperature became normal in 4 days. One patient continued to be a typhoid carrier in spite of doses of 2 Gm. of chloromycetin.

The following conclusions can be drawn from these published cases:

1. Chloromycetin constitutes the best treatment for typhoid and paratyphoid fevers.

2. Up to the present time it is the only truly specific antibiotic for these affections.

3. Chloromycetin acts much better and more surely prevents complications when it is administered early in the disease. If given during the first week anatomopathologic lesions do not have time to develop.

4. It seems that chloromycetin plays a bacteriostatic rather than a bactericidal role.

5. The development of an agglutinating power in the blood serum seems to indicate that a natural immunity develops in the same manner as in cases evolving normally.

6. Chloromycetin does not seem to create resistant strains.

7. None of the clinical cures up to the present time have brought into evidence any toxicity which could be attributed to chloromycetin administered by mouth.

8. The very early maximum concentration in the blood and the rapid excretion require frequently repeated doses (at intervals of 2 to 4 hours).

9. The parenteral route being excluded on account of disagreeable local reactions, the only possible route of administration is by mouth. If children are unable to swallow the capsules, administration by rectum should be tried.

10. The dose to be used in average cases is 50 mg. per Kg. of weight, to be given by mouth in 3 doses at intervals of 1 hour followed by doses of 25 cg. every 3 hours at first then every 4 hours until the patient remains without fever for 5 days.

11. In the classic complications the American authors advise associating the chloromycetin with penicillin or streptomycin.

The Effect of Dicumarol upon the Mortality and Incidence of Thromboembolic Complications in Congestive Heart Failure — Anderson, George M. and Hull, Edgar — *American Heart Journal*, 39: 697 (May) 1950.

Recognition of the frequency and seriousness of thromboembolic complications in congestive heart failure led the writers to study a series of cases in which dicumarol was given to half the patients and withheld from the rest.

"Dicumarol administration was begun within 24 hours of admission in the usually accepted dosage with usual precautions, the aim being to maintain plasma prothrombin activity between 10 and 30 per cent of normal throughout the hospital stay."

"Of the 297 patients whose plasma prothrombin was normal or near normal, 147 fell by lot into the treated group, 150 served as control subjects. The two groups proved to be closely similar in the distribution of cases according to etiology (with the exception of a comparative predominance of congenital heart disease in the treated group), age, sex, race, and severity of failure. The incidence of auricular fibrillation was almost the same in the two groups — 25 per cent in the treated patients, 22 per cent in the control subjects."

It was not possible to obtain trustworthy data regarding the number of bouts of failure sustained by many of the patients or the date of onset of the initial symptoms, but in an attempt to get at least minimal information regarding the time factor, the

groups were broken down according to the time elapsed since the first admission to hospital for congestive heart failure. Again, the groups appear similar: in the treated group, 32 per cent of the patients had first been admitted a year or more before they fell into the writers' series, and in 68 per cent the first admission dated back less than a year; corresponding figures for the control group were 29 per cent and 71 per cent.

"Effects of Dicumarol.—Adequate reduction of plasma prothrombin activity (10 to 30 per cent of normal) was attained in approximately 90 per cent of the 147 patients treated with dicumarol, usually within 48 to 72 hours.

"Menadione was given to 12 patients in whom prothrombin activity had fallen below 10 per cent of normal. Microscopic hematuria was noted in several patients, and in 1 there was gross but not serious bleeding from the bladder. Transfusions were not given to any of the patients.

"Mortality.—There were 11 deaths in the treated group, a mortality of 7.5 per cent. In the control group there were 20 deaths, a mortality of 13.3 per cent.

"Fatal Thromboembolism. — Autopsy was obtained in only 3 patients in the treated group; in none of these were thrombi, emboli, or infarctions found. There were 8 deaths in which autopsy was not permitted. In none of these patients were there definite clinical signs of thromboembolic complications, although 1 patient died rather suddenly in a shocklike state on the eighth hospital day.

"Autopsy was obtained in 10 of the 20 patients who died in the control group; in 8 of these evidence of thrombosis or embolism was found, and in 7 recent infarction of the brain, bowel, lungs, or myocardium appeared to have played a major role in the death of the patients. Of the 10 patients in whom autopsy was not permitted, 2 had presented definite clinical signs of severe pulmonary embolism shortly before death, and in 4 others death was rather sudden and unexpected.

"Nonfatal Thromboembolism.—One patient who fell into the treated group had evidently sustained a pulmonary embolism of moderate severity shortly before admission; in 2 others of this group definite clinical signs of acute pulmonary infarction appeared during the first 48 hours after admission, in each instance before plasma prothrombin activity had been reduced to a 'therapeutic level.' These 3 patients recovered.

"In 2 of the control group clinically recognizable nonfatal acute pulmonary infarction occurred; dicumarol was used in the treatment of 1 of these patients who nevertheless remains in the control group.

"Total Incidence and Mortality of Thromboembolism.—The incidence of definite or proved thromboembolic complications is quite low in this series—2 per cent in the treated patients, 8 per cent in the control subjects. No fatalities are definitely ascribable to thromboembolism in the treated group, but it is reasonably certain that thromboembolic complications were major or principal factors in the death of 9 subjects of the control group—almost half of the deaths in this group."

"The data suggest that the carefully controlled use of anticoagulants may improve considerably the chances of recovery from individual bouts of congestive failure."

The Failure of Antihistaminic Drugs to Prevent or Cure the Common Cold and Undifferentiated Respiratory Diseases — Feller, A. E., Badger, George F., Hodges, Richard G., Jordan, William S., Jr., Rammelkamp, Charles H., Jr. and Dingle, John H. — *New England Journal of Medicine*, 242: 737 (May 11) 1950.

The procedures employed and the results obtained in the two studies which comprise this paper are presented below under separate headings.

"Use of Antihistaminic Drugs in Naturally Occurring Respiratory Infections in Families.—For the past two years the occurrence of illnesses has been continuously observed in a population of families. During December, 1949, and January, 1950, the voluntary use of antihistaminic drugs by members of some of these families provided an opportunity to assess the therapeutic value of the drugs under well defined circumstances."

"The cases of respiratory disease on which the subsequent analyses are based were classified as follows:

Table 1. Antihistaminic Drugs Used in Naturally Occurring Respiratory Infections.

Drug	Trade Name	No. of Illnesses
Thonzylamine hydrochloride	Anahist, Neohetramine, Resistabs	55
Chlorprophenpyridamine maleate	Chlor-Trimeton, Coricidin	13
Tripelennamine hydrochloride	Pyribenzamine	8
Diphenhydramine hydrochloride	Benadryl	3
Prophenpyridamine	Inhiston	3
Chlorocyclizine hydrochloride	Perazil	1
Pyranisamine maleate	Neo-Hist	1
More than one drug		2
Unknown		1
Total		87

"Common Cold: An acute respiratory illness characterized by symptoms and physical signs referable predominantly to the nasal passages (rhinorrhea, sneezing and nasal obstruction), with or without such symptoms as fever, lacrimation, irritation of the throat, hoarseness and cough. The duration of such illnesses varied from less than 24 hours to more than 7 days. This category thus includes mild, moderate and severe common colds.

"Undifferentiated Respiratory Diseases: Questionable Respiratory Disease (?RD). The occurrence of a single symptom, such as rhinorrhea, sneezing, irritated throat or cough, for periods varying from less than one day to several days.

"Acute Respiratory Disease (ARD). An acute respiratory illness characterized by prominence of symptoms and signs referable to the throat and lower respiratory tract with or without involvement of the nasal passages. Fever and constitutional symptoms are usually present, but may be absent. This disease may differ etiologically from the common cold.

" 'Obscure' Respiratory Disease. An acute respiratory illness differing in its characteristics from the above groups sufficiently to require separate classification.

"Illnesses diagnosed as bacterial infections (streptococcal tonsillitis and pharyngitis, pneumococcal pneumonia and so forth), nonstreptococcal exudative tonsillitis and pharyngitis and primary atypical pneumonia were excluded from the present analysis.

"There were no cases of hay fever or allergic rhinitis recognized as such during the two months of the study. Asthma occurred twice—once in conjunction with a respiratory infection."

Influenza virus was not isolated from any patient, nor was epidemic influenza recognized during the study.

"The diagnosis of each respiratory illness was made by the physician observing the patient and was based on the combined data afforded by the family's records, the physician's observations, the field worker's reports and the results of pharyngeal cultures and special examinations. Uniformity of diagnosis was sought by a review of all records by one physician; any disagreement in diagnosis was resolved by discussion after reevaluation of the illness."

"In almost all cases the drugs employed were purchased over the counter and were used in single doses of 25 mg. or equivalent amounts. The number of illnesses in which each drug was used is given in table 1.

"There was considerable individual variation in the dosage of antihistaminic drugs taken, and some variation in the promptness with which medication was started after the appearance of the first symptom. The following definitions were therefore adopted:

"(*a*) 'Adequate' dosage: three or more doses taken, with medication beginning on the same calendar day as the onset of the first symptom; each dose equivalent to 25 mg. or more for adults and 10 mg. or more for children.

"(*b*) 'Inadequate' dosage: less than three doses taken, or medication started on the second calendar day of symptoms or thereafter.

"(*c*) No antihistaminic medication."

"During the two month period of observation, 376 respiratory illnesses occurred in 203 of the 253 persons comprising the 55 families. Eighty-seven illnesses were treated with antihistaminic drugs, and 289 were not so treated. Clinical classification showed that three fourths of both the treated and control illnesses were compatible with a diagnosis of the common cold. The remaining undifferentiated respiratory illnesses were likewise proportionately divided, except for the 5 cases of 'obscure' illness. These 5 illnesses occurred in children under the age of 6 years; 1 was of a single day's duration, the others were of seven or more days' duration. With this exception, the age-specific occurrence of the treated and control illnesses was similar. Such comparability permits the direct comparison of the treated and control illnesses with respect to the effect of the drugs on the illnesses. Furthermore, it indicates that the administration of the drugs did not alter the clinical picture sufficiently to influence the pattern of diagnostic classification.

"Consideration of the allergic background showed that approximately a fifth of the illnesses occurred in persons who had histories of 'respiratory allergy' and that more than a third of these illnesses were treated with antihistaminic drugs. In contrast, slightly less than a fifth of the illnesses in the 'nonallergic' persons were so treated. This tendency held true for all age groups. The difference between the treated and control illnesses is in a direction that should weight a comparison of them in favor of a beneficial effect from the use of the drugs if some of the illnesses had been allergic rather than infectious. Analysis of the duration of the illnesses in patients with an allergic background, however, showed that both their treated and untreated illnesses were of the same duration.

"Comparison of the duration of all treated and control illnesses shows that the antihistaminic drugs had no beneficial effect, regardless of whether the dosage was 'adequate' or 'inadequate.' Similarly, no benefit was seen in the common cold or in the other undifferentiated respiratory illnesses. Likewise, the duration of nasal symptoms was not abbreviated by the antihistaminic drugs. Moreover, no beneficial effect of the drugs could be shown when 'adequate' dosage was defined as eight or more instead of three or more doses.

"Finally, comparison of the duration of treated and untreated illnesses in the same person should eliminate the factor of individual variation in the response to respiratory infection. Thirty-two patients had two or more respiratory illnesses during the period of observation, at least 1 of which was treated and 1 or more was not treated. Again, it was impossible to detect a significant difference between the durations of the treated and untreated illnesses.

"It is concluded from these data that the antihistaminic drugs, as their use was observed in this population, were ineffective as therapeutic agents for the common cold and other undifferentiated respiratory illnesses.

"Effect of Antihistaminic Drugs on Common Colds Developing After Inoculation of Volunteers.—The second study was designed to evaluate the prophylactic and therapeutic effect of two antihistaminic drugs, Pyrrolazote and Neohetramine, on the occurrence and subsequent course of common colds developing after the experimental inoculation of normal volunteers."

"The inoculum consisted of nasal secretions and washings from a single donor who had a typical severe common cold beginning on October 24, 1948. The illness was characterized by sneezing, nasal obstruction, profuse watery nasal discharge, hoarseness and headache. There was no fever. The acute symptoms lasted for five days and were followed by a period of approximately two weeks during which there were thick nasal discharge, cough and sputum. The secretions were collected on the second day of illness when nasal discharge was profuse and serous; they were diluted 1:10 in sterile skimmed milk, frozen at –76° C. and stored at –20° C. Cultures on horse blood agar, sheep blood agar, and Loeffler's medium and the intraperitoneal inoculation of mice yielded only *Staphylococcus aureus* in small numbers.

"The inoculum had been shown to be infectious in two experiments in volunteers performed for another purpose; in both experiments approximately 60 per cent of those inoculated developed definite colds.

"For the first experiment in the present study (December 14, 1949), the inoculum was a 1:10 dilution of the nasal secretions. Part of this pool was refrozen and stored at −70° C. until the second experiment (February 13, 1950), at which time additional sterile skimmed milk was added to make a final dilution of 1:20. Sterile skimmed milk was employed as a control inoculum in the second experiment."

"Pyrathiazine hydrochloride (Pyrrolazote), in doses of 50 mg. four times daily, was employed in the first experiment; an inert placebo served as the control drug. Administration was started two hours before inoculation and was continued for five days.

"Thonzylamine hydrochloride (Neohetramine), in doses of 50 mg. four times daily, was employed in the second experiment; an inert placebo, indistinguishable in appearance, served as the control drug. Administration was started so that three doses were taken before inoculation and was continued for five days."

"Volunteers in the first experiment consisted of 12 medical students and 6 members of the staff. The 31 volunteers in the second experiment were medical students. Only persons who had been free from colds for at least two weeks were accepted, and most had not had a cold for a considerably longer period. A history and local physical examination excluded volunteers with chronic respiratory symptoms. Grouping of the volunteers to receive nasal secretion, sterile milk, the antihistaminic drug or the placebo was made on the basis of numbers assigned at random.

"The volunteers were given the inoculum by dropping of 0.25 cc. into each nostril. So far as possible the inoculum was retained in the nose or nasopharynx for 10 minutes. The volunteers then pursued their usual activities and kept daily records of their symptoms on forms provided them. Each volunteer was interviewed daily for at least six days by a physician who separately recorded the symptoms and examined the upper respiratory tract. Illnesses developing later than six days after inoculation were excluded from consideration.

"The volunteers were bled at the beginning of the experiments and two or three weeks later. Paired serums were examined for antibodies to the influenza viruses (PR8, FM1 and Lee strains) by the agglutination-inhibition test. No fourfold or greater increases in titer were found. Pharyngeal cultures obtained at the time of inoculation revealed no important respiratory pathogens."

"The daily records of the volunteers and of the physicians were employed for evaluation of the illnesses. The following clinical classification was employed:

"Definite Cold: Defined by the criteria given above for the diagnosis of the common cold occurring naturally in families.

"Questionable Mild Cold: Presence of a symptom or symptoms, usually nasal stuffiness, slight throat symptoms or slight headache, without definite physical signs.

"No Cold: No respiratory symptoms over and above those usually experienced by the subject.

"The nature of the observations permitted the subdivision of definite colds on the basis of severity of certain symptoms, as follows:

"Mild Cold: Definite but mild symptoms of a cold, with no constitutional reaction.

"Moderate Cold: Considerable nasal discharge, irritated throat and sometimes cough, headache and mild constitutional symptoms.

"Severe Cold: Profuse nasal discharge, marked nasal obstruction, definite or severe constitutional symptoms.

"Questionable mild colds were considered as 'no cold' for the purposes of the study.

"Classification was made independently by two physicians, who compared their results, resolved any differences and recorded the final decision without knowledge of the nature of the inoculum or medication received by the volunteer. The question of whether or not an illness should be classified as a definite cold required a compromise decision only once. In this case, one physician changed his independent diagnosis from questionable mild cold to a final diagnosis of mild cold.

"Incubation period was the elapsed time between inoculation and appearance of the first symptom. The duration of a cold was taken as the number of calendar days from onset of illness to the disappearance of abnormal symptoms. The duration of a particular symptom was the number of

calendar days on which the symptom was present."

"The administration of antihistaminic drugs in doses of 50 mg. four times a day failed to prevent the development of colds, despite the fact that medication was started before inoculation and was continued for several days thereafter. In the first experiment there were equal numbers of definite colds in the groups that received the antihistaminic drug and the placebo, respectively. In the second experiment there were 6 definite colds in the treated group and 3 definite colds in the placebo group. Eleven volunteers in the second experiment were inoculated with sterile milk; 3 developed colds; 2 of these were taking the antihistaminic drug."

"The antihistaminic drugs had no favorable effect on the severity of the illnesses, the duration of symptoms or the length of the incubation periods."

"No appreciable differences in the duration of nasal symptoms, throat symptoms or cough were found in the 14 colds treated with the antihistaminic drugs in comparison to the 10 colds treated with placebos."

"In the first experiment, volunteers were not given a sterile inoculum to test the frequency of occurrence of naturally acquired colds. During the period of the experiment an epidemic of colds was not in progress in the population from which the volunteers were drawn.

"In the second experiment, 11 volunteers were inoculated with sterile milk, and 3 subsequently developed colds. The other 8 subjects had no abnormal symptoms. A questionnaire survey of the rest of the class of 80 students revealed that 12 of them developed colds during the first six days of the experiment. Thus, an epidemic of natural colds was occurring during the second experiment."

As for side reactions, in the first experiment 2 volunteers noted mild diarrhea; both had received the placebo. "In the second experiment 2 volunteers noted mild diarrhea, and both had received Neohetramine; of 4 volunteers reporting drowsiness, 2 had received Neohetramine, and 2 had received the placebo."

"At the end of the experiments the volunteers were questioned regarding the tablets they had received. Forty-two had taken the tablets on schedule; 5 had failed to take one dose, and 2 had failed to take two doses on schedule. Of these 7, 4 had received antihistaminic drugs, and 3 had received placebos. The volunteers in the second experiment were also asked whether they had received an antihistaminic drug or a placebo; 27 were not able to identify their medication; 3 had noted a bitter taste and believed correctly that they were receiving the antihistaminic drug; 1 believed he was receiving the placebo because it was not bitter. Only 1 of these 4 developed a cold, and he had taken the antihistaminic drug."

Medical Hazards of Beryllium — ROYSTON, G. RIDDELL — *Practitioner*, 164: 391 (May) 1950.

" 'Beryllium and its salts are toxic and produce in man acute pulmonary, chronic pulmonary, dermal and systemic manifestations. There is abundant epidemiologic, clinical, pathologic and experimental evidence to support the thesis that the beryllium ion is toxic to man.' "

"Nasopharyngitis and tracheobronchitis result from exposure to fumes and invariably precede pneumonitis but often occur independently. If the exposure is sufficiently severe the symptoms may come on within a few minutes, but in the concentrations commonly met with, symptoms do not usually occur for a few days. Irritation of the eyes and nose with tightness felt across the front of the chest and a dry hacking cough that may resemble whooping cough are the chief complaints. They clear up promptly when the exposure ceases."

Acute pneumonia may be fulminating and occur within a few hours of exposure, but more commonly has an insidious onset some weeks or months later but while the subject is still exposed to beryllium. "In this way it differs from the delayed pneumonitis or chronic pulmonary granulomatosis, as it is now called, which comes on some time after exposure to beryllium has ceased. The chief symptom is exertion dyspnoea, which is usually associated with weakness, an unproductive cough, some tightness in the chest and mild malaise. The respiratory rate is often raised and may be markedly so. Fever is not characteristic but the pulse rate is increased. The

dyspnoea is out of all proportion to the physical signs, which are usually limited to a few scattered rales accompanied in the more severe cases by cyanosis. The vital capacity is decreased to as low as 40 per cent of normal. A certain amount of bronchial spasm is common. Cyanosis may be severe."

"The x-ray appearances show three stages. "Stage I, a fine diffuse granularity which under a reading glass resembles a sandstorm effect. There is no increase in the linear markings. Stage II, the addition of a diffuse reticular pattern to the appearances in stage I. Stage III, the appearance of distinct nodules, from 1.5 mm. to 2 mm. in diameter, evenly distributed throughout the lung fields, in addition to the previous changes." The appearances in stage I are pathognomonic of beryllium. "If the patient recovers, the x-ray appearances gradually regress and become normal. There is no residual fibrosis. These changes may precede the symptoms and usually outlast them, but exceptions to this are common.

"Laboratory investigations are unremarkable. Evidence of tuberculosis or syphilis has not been found. The erythrocyte sedimentation rate is only slightly increased and the blood chemistry is normal. There is sometimes mild polycythaemia and some increase in the haemoglobin level. Albuminuria has been reported."

Gross tissue findings at autopsy show that the lungs were heavy and had lost their elasticity. "The cut surfaces were homogeneous and a moderate quantity of thin fluid could be expressed. The pulmonary and peritracheal glands were soft, fleshy and moderately enlarged. The histology revealed a mononuclear exudate and the early formation of new connective tissue. . . . Apart from the lungs the other viscera were normal, except for hepatic centrilobular necrosis in 1 case which also showed several areas of coagulation necrosis of the vertebral bone marrow."

Treatment is symptomatic. "Oxygen therapy may be needed in the more severe cases. The sulphonamides and the antibiotics are useless. The antihistamines have been found useful by some workers but probably do not affect the course of the disease. Prognosis is quite good but will depend upon the degree of exposure and the individual sensitivity of the patient. The mortality is probably less than 1 per cent."

The symptoms of chronic pulmonary granulomatosis are much the same as for acute pneumonitis but, in addition, weight loss is marked and accompanied by anorexia. "A nasty taste in the mouth may also be present. Dyspnoea is very prominent, together with fatigue. Haemoptysis has been reported. Diminished vital capacity, orthopnoea with raised respiratory and pulse rates and scattered sibilant rales are the most common signs. Cyanosis is present in severe cases, together with emaciation. Fever is usually low grade unless secondary infection sets in, but this is uncommon except in the later stages. An electrocardiogram may show hypertrophy of the right side of the heart."

X-ray appearances do not differ from those in acute pneumonitis. "A miliary appearance may occur in either the acute or the chronic form of the disease." The radiological differential diagnosis may be difficult, and uncomplicated silicosis is indistinguishable from the nodular stage of beryllium granulomatosis. "Miliary tuberculosis shows the nodules but does not show the finely granular background of the beryllium condition. Virus pneumonitis, erythema nodosum, Boeck's sarcoid, the pulmonary mycoses, generalized carcinomatosis, the pulmonary appearances in radiator and boiler finishers who inhale a dust containing carbon, iron and silica, chronic welders' disease and workers with tremolite talc powder may all require differentiating from beryllium conditions."

"Chronic cor pulmonale has been frequently noted and may be the cause of death. Secondary infection may occur, but is late rather than early."

Chronic pulmonary granulomatosis is usually a severe illness of long duration, and in 36 cases followed up for from two to seven years, 6 had died, 12 were completely disabled, 11 were disabled, 3 were working and 4 were asymptomatic. "The latter 4 had been discovered by routine x-rays and had always been symptom free. The mortality is probably in the region of 10 per cent."

"The diagnosis depends upon establishing some degree of past or present contact with beryllium and bearing in mind the possibility of the beryllium diseases when

confronted with an obscure pneumonitis or miliary x-ray appearances that do not appear to fit clinically with miliary tuberculosis. The estimation of beryllium in the urine may be useful in nonoccupational cases. . . . Beryllium can also be demonstrated in autopsy material by special techniques. Acute pneumonitis has to be differentiated from acute bronchiolitis and miliary tuberculosis.

"No specific treatment has as yet been discovered. Oxygen is useful in the presence of cyanosis, and the antihistamine drugs may help bronchial spasm. The antibiotics should be given for secondary infection."

"Beryllium affects the skin in two main ways. In the first place there is a contact dermatitis from the soluble salts, which is characterized by an oedematous papulovesicular eruption chiefly over exposed surfaces. It is accompanied by considerable pruritus and there may be weeping. The element of individual hypersensitivity undoubtedly influences the time of appearance and the extent of the dermatitis. About 25 per cent of new employees have been found to be sensitive within 3 to 10 days of exposure. The antihistamine drugs have been tried with some success."

"The second type of skin lesion is the beryllium ulcer or granuloma. This is due to the implantation of a crystal of a beryllium salt into or under the skin. The most common way for this to occur is from the breaking of strip lighting tubes, when small fragments of glass, coated with a phosphor, penetrate the skin. The resulting lesion either fails to heal or a scar similar in appearance to a keloid forms and later breaks down. The lesion consists histologically of granulomas of sarcoid type. These granulomas are both simple and conglomerate. The larger ones are surrounded by concentric collagenous fibers, and in the centres of many are pale areas consisting of coarse hyaline fibres. The main cellular elements resemble epithelioid cells. Lymphocytes and multinucleated giant cells of Langhans' type are also present.

"A similar type of skin lesion is that which may accompany chronic pulmonary granulomatosis. These have been described on the dorsum of the hand, and histologically showed sarcoid-like lesions indistinguishable from those appearing in the lungs. . . . Treatment is excision of the lesion, which is always followed by healing by first intention."

"Clearly, whenever possible, harmless substitutes for beryllium should be used. Considerable success in this direction has been achieved in the fluorescent lamp industry . . . . by the introduction of halophosphates which contain no beryllium. When beryllium must be used, as in certain alloys, much has been done to diminish the hazard of inhalation and direct contact. Such measures include exhaust ventilation and the wearing of masks by operatives. Protective clothing has been made available and clean overalls should be issued daily. Both these latter should be discarded before meals. Adequate washing facilities should be provided before meals and at the end of the shift. Regular medical examinations with periodic chest x-ray examinations also help to detect early cases, and it is probably wise to limit the choice of worker to those in whom there is no history of chronic respiratory infection. All preventive measures should be taken in the firm's time and under supervision. The worker should also receive instruction in the risks involved and in the methods of prevention."

Fluorinated Table Salt in the Prophylaxis of Caries — Wespi, H. J. — *Schweizerische medizinische Wochenschrift*, 80: 561 (June 3) 1950.

From many studies it may be considered as an established fact that the incidence of dental caries is relatively low in areas where the drinking water contains about 1 mg. of fluorine per liter; with a decrease of the fluorine level of the water the incidence of caries increases, while phenomena of fluorosis with mottled enamel may occur where the water contains more than approximately 2 mg. of fluorine per liter. It seems suggestive then to try to decrease the caries incidence in areas with a low fluorine content of the water by increasing the latter, several such studies having been carried out in the United States. Dentists have successfully started prophylactic treatment of the teeth of school children with fluorine solutions, and fluorine tablets have been marketed for prophylaxis of caries.

The close chemical relationship between fluorine and iodine suggests a comparison of the iodine prophylaxis of goiter and the fluorine prophylaxis of caries. Such a comparison shows that the present situation of caries prophylaxis resembles that of goiter prophylaxis about 30 years ago when tablets and iodine addition to the drinking water were used. The use of iodized salt later proved particularly suitable for goiter prophylaxis and the question may be raised whether the use of fluorinated salt might not be the most rational form of caries prophylaxis.

The author has used a particularly intensely iodized salt for goiter prophylaxis in pregnant women for a long time, and he started to add fluorine and traces of bromine and arsenic in 1946. His preparation contains 20 mg. of potassium iodide, 100 mg. of sodium fluoride, 100 mg. of potassium bromide and 5 mg. of potassium arsenite per Kg. The uniform distribution of the additional substances in the salt can be determined readily with Eggenberger's reagent by means of a colorimetric method; this reagent contains 2 drops of 25 per cent sulfuric acid and 4 drops of 0.5 per cent sodium nitrite in 10 cc. of a 1 per cent water-soluble starch, must be prepared freshly, and produces a blue color when dropped on iodized salt, the intensity of the color affording a determination of the iodine concentration. For individual preparation of an iodized and fluorinated salt the author suggests to dissolve 0.2 Gm. of potassium iodide and 1.0 Gm. of pure arsenic free sodium fluoride in 200 cc. of water, and to pour 20 cc. of this solution on 1 Kg. of salt, mixing thoroughly in a wide earthenware dish. In the author's opinion for individual use the dose of fluorine may be doubled, so that 1 Kg. of salt contains 200 mg. of sodium fluoride corresponding to 90 mg. of fluorine.

Up to now this preparation has been given predominantly during the last months of pregnancy and therefore the period of its intake is not sufficient to allow conclusions as to caries prophylaxis. Only the author's own children received the preparation for a longer period of time. The average daily fluorine intake with this preparation can be estimated at 0.15 mg. for a child, that is considerably less than the probable optimum of about 1 mg. Teeth spontaneously lost by the author's children after 12, 13, 14 and 25 months of the use of the salt, contained in their ash 5.3, 2.2, 8.7 and 5.0 mg. per cent of fluorine respectively while a tooth surgically removed after 25 months contained 6.8 mg. per cent. The average fluorine content of the ash of teeth in the author's locality amounts to 4 mg. per cent. At the time of the onset of the salt administration, these teeth had already been completely formed; as the values found were mostly above the average, it seems likely that the teeth take up fluorine from the blood when the supply is increased. Thus fluorinating the salt would be a technically simple and effective procedure resulting in an increased fluorine uptake of the teeth and in increased resistance to caries.

Some authors considered the question of thyroid inhibition by fluorine and therefore the possibility of goiter production by fluorine administration. Among the newborns of 72 women not subjected to the increased prophylaxis the author found a normal thyroid gland in 56 cases, palpable lateral lobes in 15 and a visible goiter in 1, while among 53 newborns of mothers subjected to the increased prophylaxis for more than four weeks, 52 showed a normal thyroid gland and only 1 a palpable lateral lobe. Thus the fortified salt had a definite prophylactic effect with respect to goiter of the newborn, and a goiter-producing effect could definitely be ruled out. If the fluorine has a goiter-producing effect in the dosage used it is abolished by the concomitant iodine prophylaxis. Whether in the presence of iodine deficiency, fluorine favors the appearance of goiter and constitutes a manifestation factor cannot be decided, on the basis of the author's data. However, in Switzerland with its danger of goiter, it would seem indicated to combine fluorine prophylaxis regularly with iodine prophylaxis.

It has been demonstrated that wholesale fluorination of the salt is technically feasible and that loss on prolonged storage is relatively low, amounting to 17 per cent after six months storage in open glass containers.

The physiologic role of fluorine is not accurately known and it is not even certain whether fluorine actually constitutes a vitally necessary substance; therefore to

date it is not justified to speak of fluorine deficiency or a fluorine-deficiency disease. Caries is a complicated problem in which growth, vitamins, other nutritional factors, chewing and bacteriologic factors play a part; therefore fluorine deficiency cannot possibly be the only decisive cause and increased fluorine administration cannot be the only possible and effective prophylactic method. It seems preferable to talk about an increase of the resistance to caries due to the fluorine rather than of caries prophylaxis. Studies to date dealt only with the fluorine concentration of the drinking water, but other foods contain fluorine, particularly the vegetables, bread and milk. In the animal body, apart from the teeth particularly, the bones contain fluorine. It may be assumed that the fluorine of water and food does not chiefly act on the teeth directly by local contact but reaches them after absorption. The daily fluorine intake should not fall below a certain minimum and in most parts of Switzerland this minimum is not normally obtained.

According to work done so far, an additional daily intake of 0.5 to 1.0 mg. of fluorine would be indicated in most parts of Switzerland. Individual and general prophylaxis must be distinguished as in goiter prophylaxis. The former is easily carried out with tablets but does not reach all individuals and the ones who need it most may not be included. The decisive factor seems to be a sufficient supply of fluorine at the time of the formation of the teeth while once the tooth is mature additional fluorine administration would be useless. Therefore in males the prophylaxis should extend from birth to about the age of 20, while females need the increased fluorine intake during pregnancy and should therefore be subjected to the prophylaxis throughout the childbearing phase. As fluorine prophylaxis is not harmful these conditions would indicate a systematic prophylaxis by addition of the fluorine to a food component which is taken in approximately the same amount by virtually the entire population; that is, water and salt, and possibly bread and milk.

Salt has the advantage over water that the entire population can be supplied from one source while in the case of water, each water supply system would have to be supplied separately which is almost impossible in rural areas. Individual variations in the salt intake are limited, but the relatively narrow therapeutic range of fluorine has the disadvantage of the necessity of a cautious dosage. It is important to decide whether only salt used at the table is fortified or also the salt used in bread, meat products, cheese and milk and that used in the kitchen.

In the case of iodine the thyroid gland is known to be the organ of storage; its contents amount to about 10 mg. of iodine; that is, the requirements for three months. Fluorine is deposited in the teeth and bones and the latter must be considered as organs of storage. It will have to be determined whether fluorine stored in the bones can be mobilized when necessary; e.g., during pregnancy for the supply of the fetus. A priori such a mobilization seems likely. Such a storage has the great advantage of compensating for variations in the fluorine intake.

With the suggested dosage of 100 mg. of sodium fluoride per Kg. of salt, production of fluorosis would seem impossible. The danger of overdosage could be avoided by making the fluorine preparation subject to prescription. Fluorosis involves the skeleton as well as the teeth and roentgenologic and anatomic controls may be indicated on introduction of fluorine prophylaxis, but mottled enamel is the first sign appearing in otherwise harmless overdosage and the main control of overdosage would fall into the field of the dentists.

If only the table salt is fluorinated a dosage of 100 to maximally 200 mg. of sodium fluoride per Kg. would seem indicated, while on fluorination of all salt a dosage of 60 to 80 or maximally 100 mg. would seem satisfactory. At the time of tooth formation; that is, in infants, children and adolescents, and in pregnant and nursing women an additional individual prophylaxis with fluorine tablets would seem indicated; these tablets might also contain calcium, potassium iodide and various vitamins. The short period of administration of this additional prophylaxis under the control of dentists and physicians in the schools would reduce the danger of fluorosis to a minimum or eliminate it completely.

The effect of fluorine prophylaxis cannot be evaluated until after several years of

observation. The fluorine storage takes place chiefly during tooth formation and the increased resistance to caries cannot be evaluated until after the teeth have come out and have been exposed to the caries-producing factors for a considerable period of time. Therefore, fluorine prophylaxis would have to be carried out in a rather large group of the population continuously for several years; in view of the skeletal storage of fluorine, chemical studies of the bones would furnish data as to dosage and possible dangers. Teamwork extending to various fields would be required to evaluate the results. In some areas of Switzerland the drinking water contains more fluorine and there, prophylaxis would not be indicated. Only after experiments in smaller areas a regulation of the fluorine prophylaxis by law could be considered. Switzerland would be a good place to pioneer in the prophylaxis of caries as it has pioneered in goiter prophylaxis.

Long Term Dicumarol Therapy to Prevent Recurrent Coronary Artery Thrombosis — NICHOL, E. STERLING AND BORG, JOSEPH F. — *Circulation*, 1: 1097 (May) 1950.

"Since 1944 dicumarol therapy has been continued indefinitely following an attack of acute coronary thrombosis and/or myocardial infarction in 78 patients in the hope of preventing recurrent attacks."

"Clinical description of 78 patients given dicumarol prophylactically for periods ranging from 3 to 62 months follows: Forty-four patients received dicumarol for 3 to 12 months, 23 for 12 to 24 months, 8 patients for 24 to 36 months, 2 for 36 to 48 months, and 1 for 62 months. There were 12 patients under 50 years of age, 34 between 50 and 60 years, and 32 between 60 and 75 years. Thirty-three patients had experienced more than one attack of coronary thrombosis. Seventeen patients were not placed on the regimen until some time after their acute attack, when, because of increasing angina or acute coronary insufficiency, dicumarol therapy was started."

"In 9 patients therapy was discontinued after 3 to 23 months—in 2 because of change in residence, in 4 because of lack of cooperation or difficulty in obtaining prothrombin determinations, and in 3 because of hemorrhagic complications. Twelve patients . . . . died while under treatment —in 4 death was due to recurrent attacks of coronary thrombosis; in 6 it was ascribed to either acute coronary insufficiency, congestive heart failure, or 'cessation of cardiac activity' (probably ventricular fibrillation or ventricular standstill). Cerebral hemorrhage was the cause of death in 2 patients. Autopsies were performed in 8 cases, revealing fresh coronary thrombosis or infarction in 3. No mural thrombi or other complicating thromboembolic manifestations were found."

In 7 of 8 autopsied patients who had used dicumarol for 2 to 23 months, no toxic changes were found in the liver or kidneys attributable to dicumarol except for the possibility that the microscopic hemorrhage in the hepatic hemangioma in 1 patient might have been due to the dicumarol, although this is unlikely. "No evidence of liver or renal injury after one or more years of dicumarol therapy has developed in the living patients."

"In the 57 patients remaining on dicumarol, anginal pain has been minimal or absent in nearly all, in spite of their being moderately active in business or home. The willingness of patients to adhere to the regimen faithfully reflects substantial subjective improvement hardly fully attributable to the psychotherapeutic effect of taking dicumarol. Four of the living patients have experienced episodes of acute coronary insufficiency with possible subendocardial infarction followed by recovery without thromboembolic complications. The clinical features of 1 exceptional case, occurring in an elderly woman who developed a third recurrent acute myocardial infarction while dicumarol was in force, follows:

"Patient Mrs. J. R., aged 63 years, had survived an attack of myocardial infarction 13 years previous to development of premonitory signs of coronary thrombosis on September 2, 1948. She was given heparin and dicumarol but continued to have cardiac pain with occasional nausea and vomiting. When the prothrombin time was 46 seconds (9 per cent PA), 15 days after onset, following severe pain, the electrocardiogram showed evidence of

anterior wall infarction. Complete relief of her pain, much of which was provoked by the gastrointestinal tract, was not obtained. By the sixth week she was able to be slightly ambulant. The prothrombin time was maintained between 20 and 35 seconds (40 to 10 per cent PA). On January 19, 1949, she had severe substernal pain when the prothrombin time was 30 seconds (18 per cent PA). The electrocardiogram showed changes indicative of acute anterolateral myocardial infarction. Congestive heart failure and various ectopic rhythms appeared, and heart failure persists four months later, but the patient is able to be ambulant at home with only mild anginal pain."

"Obviously dicumarolization did not forestall a recurrent attack, and her case demonstrates that the regimen even when carefully followed may fail to prevent coronary thrombosis.

"Eleven patients have followed the regimen two years or longer without recurrence although 6 had multiple previous attacks."

"Hemorrhagic manifestations occurred in 28 patients, in 13 of whom hemorrhage was of major type. Hemorrhage occurred in some patients in more than one site and on more than one occasion. It is to be expected that patients taking dicumarol for months or years should experience more episodes of hemorrhage than patients taking dicumarol for a few weeks only." Two fatal hemorrhages were encountered. "One occurred in a 63 year old man who had three attacks of coronary artery thrombosis and died after eight months of dicumarol therapy with massive cerebral hemorrhage due to rupture of the right lenticulostriate artery. The other took place in a 72 year old hypertensive man with coronary artery disease and congestive heart failure, who, after two months of dicumarol therapy, died in coma and convulsions due to petechial hemorrhages in the internal capsule and pons.

"In only 3 patients was it necessary to abandon the dicumarol regime because of hemorrhage: In 1 of these patients repeated hematuria associated with urologic disease occurred after five months of therapy; in another hemorrhage into the shoulder joint followed automobile injury after 23 months of therapy; in the third, massive, silent gastrointestinal hemorrhage occurred after 13 months of therapy. This last patient was a Greek man with an alcoholic history. Gastrointestinal x-ray studies and liver function studies showed no abnormality when his prothrombin time reached 60 seconds (6 per cent PA), following an increase in his weekly dosage from 400 mg. to 500 mg. during a period of increased consumption of alcoholic beverages. An episode of hematuria had occurred three months previously in this patient when the prothrombin time was 35 seconds (15 per cent PA), yet no hematuria developed at the time of the gastrointestinal hemorrhage in spite of the prothrombin activity being only 6 per cent, which shows the unpredictability of dicumarol-induced bleeding.

"Hemorrhagic episodes are not always well correlated with the prothrombin activity. Bleeding may occur in some patients when the prothrombin activity is only moderately reduced, and on other occasions in the same patient bleeding might not occur with considerably less prothrombin activity. Adequate amounts of synthetic vitamin K given intravenously controlled the bleeding and lowered the prothrombin time, except in 2 patients requiring transfusions. The risk of hemorrhage in anticoagulant therapy, and the obligation of the clinician to make sure that the laboratory understands the technical pitfalls of prothrombin determinations, have been stressed repeatedly in the literature."

Although it has been known since earliest clinical use of dicumarol that the dosage required for producing effective hypoprothrombinemia is variable, it is not so well known that in long term dicumarol therapy marked disparity in the weekly requirement of dicumarol by different patients may occur.

"Of 3 patients receiving dicumarol for 52 weeks, 1 required approximately 225 mg. per week, another 500 mg. per week, and a third 950 mg. per week, to maintain the prothrombin concentration between 30 and 10 per cent of normal (24 to 38 seconds). Even more important is the sudden change in a patient's tolerance that may occur after many months of dicumarol therapy."

Chloromycetin in the Therapy of Granuloma Inguinale — GREENBLATT, ROBERT B., WAMMOCK, VIRGENE S., DIENST, ROBERT B. AND WEST, ROBERT M. — *American Journal of Obstetrics and Gynecology*, 59: 1129 (May) 1950.

"Streptomycin was employed in the therapy of 142 patients with granuloma inguinale. A cure rate of 86.6 per cent was obtained with a single course of treatment. The average effective dose was 20 Gm. administered intramuscularly in 1 Gm. doses every six hours for five days. In the 19 failures the initial dose was inadequate in 6, being 10 Gm. or less. Fourteen who failed to obtain a cure following the first course responded successfully to a second course of treatment. There were only 5 patients who proved to be streptomycin resistant, a failure rate of 3.5 per cent. All of the streptomycin-resistant patients, however, proved responsive to aureomycin therapy. The advantage of streptomycin therapy is the shortness of the period necessary for treatment; i.e., five days. The disadvantage is the need for hospitalization.

"Aureomycin has been used in 46 patients. Intramuscularly, in doses of 250 mg. every four hours for totals of 800 to 1,500 mg., the drug proved ineffective. Orally, this antibiotic proved most efficacious. The lesions in the 5 streptomycin-resistant patients were healed with oral aureomycin and the lesions in most of the other patients responded readily." With the use of this antibiotic as little as 5 Gm. were used in doses of 250 mg. every four to six hours. "The lesions healed superficially but Donovan bodies could be demonstrated deep in the tissues after apparent healing. Breakdown occurred in each instance and the dosage was stepped up so that the average patient received 20 to 30 Gm. in doses of 500 mg. every 6 hours for 10 to 15 days. In this series the smallest dosage used that effected a cure was 10.8 Gm. and the largest dose required was 70 Gm. In this latter instance the patient had extensive lesions measuring some 300 sq. cm. in size. The patient proved resistant to three courses of streptomycin in which a total of 158 Gm. was used. Although complete healing was obtained with 50 Gm. of aureomycin, another 20 Gm. were added as insurance against a relapse. Though 20 to 30 Gm. of the drug appear to be sufficient for the average case, it was found that patients with extensive lesions or with slowly responsive lesions required from 40 to 70 Gm. In several instances, healing was incomplete after one course of therapy and a second course was given. Only 2 relapses have thus far been observed in patients who had healed after receiving 20 Gm. or more of the drug. In these instances successful responses were obtained on retreatment. The patients in this series have now been under observation from 1 to 10 months. Half of them have been followed for at least five months. Toxic reactions such as nausea, vomiting, and diarrhea have been encountered in several of the patients with 500 mg. dosage, and much more frequently when the dosage was stepped up to 1 Gm. every six hours.

"Chloromycetin is the antibiotic now under scrutiny. Between March 18, 1949 and September 16, 1949, therapy with this antibiotic was employed in 23 women patients. The dosage at first was chosen arbitrarily at 20 Gm. One-half gram every six hours was administered over a period of 10 days to 4 patients. The response was striking. One gram was administered every six hours over a period of five days to the 4 other patients. The results appeared equally good. In each group there was 1 case with incomplete healing and a second course of therapy was necessary before complete healing occurred. Two patients were treated with 70 and 40 Gm., respectively. It appeared that that dosage was required for complete healing in patients with extensive lesions; hence the variance in dosage. Most of these patients have now been followed for four to six months. The results are most promising. Untoward effects have not been noted. Two relapses occurred and these patients responded to a second course of Chloromycetin. Donovan bodies disappear from the lesions more rapidly than with aureomycin or streptomycin. The advantages of its use are that it may be administered on an outpatient basis and that it is not toxic. When administered to hospitalized patients the disadvantage is the length of time required for treatment; i.e., 10 to 20 days."

"Other antibiotics have been tried. Penicillin proved ineffective, tyrothricin used locally and bacitracin used in the form of suppositories proved valueless. In this connection, it may be stated that streptomycin suppositories were used in 7 cases and proved effective in 4."

A New Test for Vasopressor Substances in Hypertension — FISHBACK, DAVID B. — *American Journal of the Medical Sciences*, 219: 517 (May) 1950.

A new test is presented for the detection of vasopressor substances in the blood serum of hypertensive patients.

"Method of Determining Normal Circulation Time in Rabbits.—Young white female rabbits are used. The animal is placed in a Cornell animal box, with the head protruding. One cubic centimeter of 10 per cent or preferably ½ cc. of 20 per cent sodium fluorescein is injected rapidly into the marginal vein of the ear. With the left hand another person holds a small portable ultraviolet light plus filter (kept turned on throughout the test) and a stop watch. The right hand turns off the room light; e.g., an ordinary lamp light. The ultraviolet light is directed toward the rabbit's eye, and the right hand is used to separate the rabbit's eyelids. The stop watch is stopped immediately upon noting a brilliant yellow color in the conjunctiva along the inner margin of the eyelids. Almost simultaneously there is a brilliant yellow color in the iris of the eye, the nostrils and the gums of the animal. The average normal circulation time in rabbits is 5 to 6 seconds.

"Effect of Drugs on Circulation Time in Rabbits.—The normal circulation time was determined for each rabbit. The fluorescein method was used to determine blood velocity at various times after intravenous administration of drugs. In most instances, caffeine, coramine, metrazol, and strychnine slightly decreased circulation time (increased blood velocity), while adrenalin, pituitrin, and to a lesser extent, neosynephrine hydrochloride and paredrine hydrobromide, lengthened circulation time.

"In human beings, the opposite result occurs. The administration of adrenalin speeds up the circulation time."

"Fluorescein has also been used to determine circulation time in humans.

"A New Test for Vasopressor Substances in the Blood of Hypertensive Patients.—A rabbit is placed in a Cornell animal box; 3 cc. of human blood serum at room temperature are injected into the ear vein; 2 to 4 cc. may be used, with 2 cc. giving lower readings. After 2 minutes, the fluorescein circulation time is determined."

"Neither warm weather nor the passage of several days' time between withdrawal of blood from the person and its injection into the rabbit interferes with the test."

Four specimens of blood serum were marked code No. 1, 2, 3, 4.

"Code 1: 4 cc. Serum—Circulation time 5.2 sec. (normal)

"Code 2: 3 cc. Serum—Circulation time 4.0 sec. (normal)

"Code 3: 4 cc. Serum—Circulation time 11.4 sec. (abnormal). Increased vasopressor substances.

"Code 4: 3 cc. Serum—Circulation time 13.0 sec. (abnormal). 1½ cc. Serum —Circulation time 8.8 sec. (abnormal). Increased vasopressor substances.

"Later data were received on these cases.

"Code 1: Normal blood pressure, pernicious anemia

"Code 2: Normal blood pressure

"Code 3: Male, white, age 42, Malignant Hypertension. B.P. 213/155. Blood Urea N. 44 mg./100 cc. Urea clearance 19 per cent of average normal. Ophthalmoscopic examination reveals papilledema, numerous hemorrhages, exudates and intense vasoconstriction with marked arteriolar sclerosis.

"Code 4: Male, white, age 52, Malignant Hypertension. B.P. 225/122. Blood Urea N. 54 mg./100 cc. Urea clearance 17 per cent of average normal. Changes in the optic fundi indicative of the onset of malignant syndrome."

"Using fluorescein intravenously, the average normal circulation time in rabbits is 5 to 6 seconds. An arbitrary dividing line between normal and abnormal circulation time in rabbits after the injection of human blood serum may be taken as 7.5 seconds. Below 7.5 seconds can be regarded as normal and above 7.5 seconds as prolonged. The presence of excessive vasopressor substances in the blood serum of hypertensive patients probably causes a peripheral vasoconstriction in the rabbit, with a resulting prolonged circulation time.

"Almost all persons with normal blood pressures yielded normal results. Whether those who gave abnormal results will later develop hypertension remains to be seen."

"Most of the cases with hypertension, especially malignant hypertension, gave abnormal results. The few that did not may have been cases of very benign type; in the future it might be of value to correlate eyeground findings, etc." In the cases of hypertension with uremia, only a slight to moderate prolongation of circulation time occurred.

"Further studies are indicated to evaluate the test in diagnosis of prehypertension, benign hypertension, malignant hypertension, pheochromocytoma, prior to and after dorsolumbar sympathectomy for hypertension, and in the diagnosis of early eclampsia."

Occupational Jaundice and Anaemia— Browning, Ethel — *Practitioner*, 164: 397 (May) 1950.

"In considering jaundice or anaemia, or a combination of both disorders, as the consequence of exposure to occupational hazards, it is necessary to examine the potentiality for injury of a large number of toxic agents, both physical and chemical, and a wide variety in the nature and degree of their effects. These effects may also be greatly influenced by nutritional deficiencies in the individual."

Agents Producing Jaundice as Their Chief Toxic Effect.—"The two most important jaundice-producing solvents of this group are undoubtedly tetrachlorethane and carbon tetrachloride. Both may attack the kidneys also; in the case of acute carbon tetrachloride intoxication nephritis is often the predominant injury, while the liver injury caused by exposure to relatively lower concentrations is much more likely to recover than is the case with tetrachlorethane."

Tetrachlorethane is a powerful solvent and is still used to some extent in degreasing, paint removal, extraction of fats and, in France especially, in the manufacture of artificial pearls. "Inhalation of large quantities may prove fatal from its acute narcotic effect before liver injury has become apparent, but its greatest hazard is the 'delayed' metabolic effect from repeated non-narcotic concentrations. The maximum atmospheric concentration now regarded as safe for continued exposure is 10 parts per million.

"Premonitory symptoms of poisoning are sometimes related to the nervous system, more often to the gastrointestinal tract—loss of appetite, nausea, vomiting, abdominal pain. After an interval lasting from three days to three months, jaundice appears, progressing to the 'toxaemic' stage, with enlarged and tender liver, delirium, convulsions and coma, leading to death with or without the stage of ascites and albuminuria. The jaundice is obstructive in nature, due to inflammation of the small intrahepatic bile ducts, followed by toxic fatty degeneration and necrosis (acute yellow atrophy).

"The course and nature of carbon tetrachloride intoxication is somewhat different. Carbon tetrachloride is widely used as a solvent, cleaner and degreaser and as a constituent of many fire extinguishers. It was at one time regarded as the most toxic of all the halogenated hydrocarbons, but recent investigations tend to show that with proper safeguards against high concentrations its effects on the liver, although often unpleasant, are neither severe nor permanent. Most of the severe cases of poisoning reported have occurred when concentrations have been well above 100 parts per million, a level which it is entirely possible and practicable to reach in most of its industrial applications. With high concentrations, such as may arise when fire extinguishers are used in a closed space, in accidental inhalations from vessels containing carbon tetrachloride, or in badly regulated dry cleaning establishments, the initial narcotic effect, although sometimes severe, may quickly disappear, but after an interval of 3 to 12 days, symptoms of involvement of the liver or kidneys, or both, arise. In the 'hepatorenal' type of poisoning the predominant feature is usually jaundice; in the 'pure renal' type, albuminuria, haematuria and anuria are the most conspicuous signs of injury.

"With exposure to lower, repeated, concentrations, the liver is not likely to be severely or permanently injured, even though symptoms of gastrointestinal disturbance may be serious enough to cause considerable ill health. This is because the toxic effect is more functional than

organic, and because regeneration of damaged liver cells takes place rapidly on cessation of exposure."

"Among the other 'poisonous substances' which may cause jaundice are the chlorinated naphthalenes and phosphorus.

"When naphthalene is chlorinated, a waxlike substance (chlorowax) is formed, which is used in industry as an insulating coat on electrical wires, or on metal to limit the action of plating processes. Inhalation, ingestion, or skin absorption of the dust or fume may produce, in addition to the characteristic skin lesion known as 'chlor-acne,' severe injury to the liver."

"Phosphorus, of which the yellow variety was once of great industrial importance and hazard in the match industry, has now been largely superseded by safer substitutes, although it is still used in the manufacture of phosphor bronze. The present infrequency of its most alarming manifestations, necrosis of the jaw ('phossy jaw') and intense jaundice, is another outstanding example of the control of toxic hazards in modern industry. Jaundice, accompanied by gastrointestinal disturbance and loss of appetite, is an early sign of phosphorus poisoning, and the liver injury is believed to be due to inhibition of glycogen formation and of normal enzymic liver function, so that while autolytic processes continue, toxic decomposition products are formed."

Agents Producing Both Anaemia and Jaundice.—Nitro-derivatives and amido-derivatives of benzene include aniline, nitrobenzene, dinitrobenzene and trinitrotoluene. These are used in the dyeing industry, as accelerators and antioxidants in the rubber industry, and to some extent in paints, perfumes and fungicides. "All have the characteristic property of forming methaemoglobin, and some, notably trinitrotoluene, of causing liver damage also. They are thus, as a group, agents which may cause both anaemia and jaundice.

"Trinitrotoluene is another highly toxic substance which has shown itself amenable to control. . . . In the production of aplastic anaemia, trinitrotoluene is unique among this group of compounds, and its action on the liver, although more important toxicologically than its methaemoglobin-producing effect, is not of such frequent occurrence. . . . Jaundice may appear, however, several weeks after cessation of exposure, or sometimes without any premonitory symptoms. In fatal cases the liver shows yellow and red necrosis with little attempt at regeneration.

"Nitrobenzene, or oil of mirbane, although it may produce jaundice, is preeminently a methaemoglobin-former, giving rise to the characteristic lilac cyanosis, and often to a very severe anaemia, but not of the aplastic type.

"Dinitrobenzene also produces severe secondary anaemia, but jaundice is unusual.

"Arsine (AsH_3), although producing jaundice, is primarily a haemolytic agent, the liver function being disturbed more as a concomitant of disintegration of red cells than by actual disorder of the liver, although this may occur.

"Exposure to arsine may occur in the process of cleaning metal tanks containing sulphuric acid, the hydrogen generated, combining with arsenical impurities in the acid; also in the pickling and galvanizing of metals containing arsenic; in soldering, etching, and electrolysis of arsenious solutions, and in the reduction of nitro bodies to amino bodies. Its toxic action is first exerted on the red blood cells, where it combines with the haemoglobin and causes haemolysis with widespread destruction of the cells. Profound anaemia rapidly supervenes and the accompanying cyanosis, combined frequently with jaundice, gives the skin a characteristic bronze colour.

"Agents Producing Anaemia Without Jaundice.—'Toxic anaemia' was made notifiable in 1942, and its definition 'is intended to apply to dyshaemopoietic anaemia occurring in a person employed in a process which brings him into contact with x-rays, radioactive substances and any chemical compound which may be capable of causing this effect.'

"It may be noted that under this definition cases of secondary or nutritional anaemia, probably having no association with occupational factors, may be included, since any variation of the normal blood picture may, in the widest sense, be regarded as 'dyshaemopoiesis.' From the point of view of diagnosing a true occupational anaemia this is of considerable advantage, since notification leads to further

investigation of any such case, and its differential diagnosis from anaemia caused by the industrial noxious agent to which the person employed is exposed. It may also be noted that the term 'toxic anaemia' gives an opportunity of notifying cases of anaemia due to exposure to benzene which could not, in the absence of 'haemorrhages under the skin and bleeding from the gums, nose and other passages in the last stages' be notified as 'chronic benzene poisoning.'

"The many toxic agents which produce dyshaemopoiesis may be classified as (1) those which act directly on the bone marrow; (2) those which act on the peripheral blood cells; and (3) those which form methaemoglobin."

Poisons Acting on the Bone Marrow: "Benzene is one of the most efficient of all organic solvents and is therefore used extensively in a large number of industries: for extraction purposes, in organic synthesis, in the rubber and water-proof industries, as a thinner in paints and varnishes, in the manufacture of artificial leather, in cleaning and degreasing. In large doses it is a powerful narcotic, but its chief importance in industrial toxicology is its chronic effect in small repeated doses. The classical effect is that of aplastic anaemia, producing complete aplasia of the bone marrow, but this is by no means an invariable picture. The most frequent blood picture of severe anaemia with a high colour index, and leukopenia, is often complicated by the fact that the depressing effect on the bone marrow is accompanied by a regenerative activity, so that compensation may mask the destruction of both red and white cells. In some cases the initial effect is a hyperstimulation with leukocytosis, while the final phase may develop into a fatal leukaemia. The experience of most workers in this field of recent years, however, shows that the most reliable deviations from the normal blood picture in the early stages of 'benzene absorption' are a fall in the total number of polymorphonuclear leukocytes, whether this be accompanied by a frank leukopenia or not, and a thrombocytopenia. The most unfortunate feature of chronic benzene poisoning is that symptoms do not go hand in hand with blood changes; it is often found that workers exposed to benzene do not complain of any disturbance of health except undue fatigue when their blood picture shows evidence of considerable damage to the blood-forming organs. It is unfortunate also, that removal from exposure, to be effective, must take place before the injury has gone too far; once the stage of haemorrhage into the skin and mucous membranes is reached, no therapeutic measures seem to prevent a fatal outcome." In the writer's experience leukopenia has been found in some cases to remain unchanged for three or more years after all exposure has ceased, and in 1 case, in a woman who had been employed for four years in painting rubber rings with a benzene rubber solution, death took place after two years of nonexposure.

"Basically the anaemia which results from excessive exposure to the gamma radiation of radium or to x-rays is a manifestation of the lethal effect of ionization on the individual cell, its cytochemistry, its chromosome development and gene mutation.

"In modern industry the use of radium and x-rays has two principal applications—the painting of dials and other instruments with 'luminous compound' containing a small amount (5 to 70 micrograms per gram) of radium salt, and the examination of castings and other articles by means of either the radium 'bomb,' a radon 'seed,' radioactive isotopes or x-rays. In all these industries such strict protective measures have been adopted that there is practically no possibility that exposure sufficient to cause a fatal anaemia could occur." Strict control of the actual dosage is now possible by the use of the Geiger counter or photographic films.

"Overexposure of any considerable degree is usually reflected in the blood picture as a depression of the polymorphonuclear leukocytes; sometimes a neutropenia only, sometimes a mild leukopenia, and since the lymphocyte is extremely sensitive both to the effect of excessive radiation and to recovery from it, the absolute lymphocyte figure may show great variations. Another pointer is the presence of abnormal cells in the stained film. These, in the form of primitive types of large mononuclear cells, have been observed most often in the stained films of the blood of luminizers.

"Poisons Acting on the Peripheral Blood: The principal example of a toxic substance acting, not on the bone marrow, but upon the cells circulating in the blood stream is lead. The mild anaemia, accompanied by the presence of 'stippled cells' or punctate basophilia, is regarded as evidence of lead absorption, prior to the development of the toxic manifestations constituting lead poisoning. Blood examinations of workers in lead processes, such as the manufacture of certain lead compounds, removal of lead-containing paints, as in ship breaking, the manufacture of electrical accumulators, and in many other industries where lead may be introduced into the body by inhalation of dust or fume or ingestion from contaminated food, are therefore of value, when combined with analyses of the atmosphere, blood, urine and faeces, in estimating the actual exposure. The significant findings are the presence of a low red cell count with a falling haemoglobin level, giving rise to a colour index below 1, and of stippled erythrocytes above the level of 1,000 per million red cells. Practically all workers exposed to lead show some punctate basophilia, which, of course, occurs in other forms of severe anaemia, but an abrupt progressive increase is strongly suggestive of lead absorption.

"The anaemia is believed to be due to the actual precipitation of lead in the red cell envelope, making it more easily destructible, so that many red cells disappear from the circulation. This is followed by a compensatory regeneration with the appearance of immature forms, represented by the young stippled cells."

Brucella Suis Infection Treated with Aureomycin. Case Report — BOAL, DELFORD H. AND ISHII, A. H. — *Journal of Missouri State Medical Association*, 47: 364 (May) 1950.

"Brucellosis is an extremely common disease in the dairy and packing industry. Treatment has been extremely unsatisfactory until the advent of streptomycin and sulfadiazine. This fairly satisfactory combination probably will be supplanted by aureomycin which is even more effective.

"The following case is reported because it illustrates the prompt response which can be expected in a proved case of brucellosis and because the causative agent was *Brucella suis*."

A 34 year old Negro male was admitted to the hospital on August 6, 1949. "He had been a packing company employee for 20 months handling fresh and frozen meats.

"Ten days prior to admission he began to have fever daily beginning at from 2:00 to 3:00 P.M. and accompanied by profuse sweats. He complained of occipital headache, malaise and weakness. Five days before admission he developed a cough which produced yellow sputum.

"He did not appear acutely ill, was oriented but lethargic on admission. Oral temperature was 101 F., pulse rate 88 per minute, respiration 20 per minute, blood pressure 130/80. The skin was warm and dry on first examination but cool and moist thereafter. Discrete, nontender lymph nodes were felt in the epitrochlear, inguinal and axillary areas. A grade II systolic murmur was heard at the apex of the heart. The liver was felt 4 cm. below the right costal margin and the tip of the spleen was felt.

"Leukocyte count was 6,750 per cc. Schilling differential count was 37 per cent segmented, 32 per cent stabs, 22 per cent lymphocytes and 9 per cent monocytes. Urine analysis showed specific gravity, 1.022; no sugar and 1 plus albumin. Microscopic examination gave normal findings.

"Chest x-ray was normal. Two blood cultures were taken on the eleventh and thirteenth days of illness and were positive for *Br. suis* in tryptose phosphate broth. Agglutinin tests for Brucella was positive in a titer of 1:160 on the eleventh day of the disease and reached a maximum titer of 1:5,120 on the fifteenth day.

"During the first six hospital days the fever followed a septic course reaching a peak of 105.2 F. on the sixth day.

"Aureomycin was started orally on the fifth hospital day with a trial dose of 250 mg. and 500 mg. was given on the sixth day. The patient tolerated the drug well and 500 mg. was given every six hours from the seventh to the twelfth day. The dose was then decreased to 250 mg. every six hours until the fourteenth hospital day when it was stopped. A total of 13 Gm. of aureomycin was given.

"Remarkable clinical improvement occurred as a result of the aureomycin treat-

ment. The temperature fell to normal in 24 hours and did not rise above 99.4 F. at any time after that and the patient felt much better. Malaise and headaches disappeared, he felt stronger and was soon up and around. On the fifteenth day, the agglutinin titer dropped to 1: 1,280. The patient was discharged from the hospital on the seventeenth day which was the twenty-seventh day of the disease.

"The patient has been completely asymptomatic for three months and has returned to his work. The Brucella agglutination titer on November 6, 1949, was positive in a dilution of 1:2,540.

"Aureomycin was of benefit, immediately and consistently, in a group of 40 patients treated in Minneapolis and in Mexico City. . . . The majority of these cases were due to *Brucella melitensis* and *Brucella abortus*. The average dose of aureomycin was 2 Gm. daily in divided doses for two weeks.

"Infections due to *Br. suis* have been treated with aureomycin, but the number of cases so treated is small."

Acute Malignant Exanthematous Lupus Erythematosus — CONTRERAS, FÉLIX — *Medicina*, 18: 237 (April) 1950.

Exanthematous lupus erythematosus was first described by Kaposi in 1872; the description was completed by Besnier and Doyón in 1891. A more detailed study of the visceral and articular symptoms of this affection was published by Osler in 1904, and Libman added participation of the endocardium in this process in 1911, coining the term of atypical verrucose endocarditis. Renal participation was also added. From 1940 on, an increasing number of reports on this diffuse systemic capillary or peripheral vascular affection has been published. The syndrome is dominated by cutaneous erythematous lesions of the type of lupus erythematosus, fever, nephritis which may pass unnoticed if it is not looked for, more or less manifest polyarthritis, polyserositis of variable localization and intensity, endocarditis which may also be clinically latent, increased sedimentation rate and leukopenia with relative lymphocytosis. Various syndromes have been described in this disease including acute lupus erythematosus or persistent facial erysipelas (Kaposi), the Libman-Sacks syndrome of disseminated cutaneous lesions of lupus erythematosus, articular and renal manifestations, and atypical verrucose endocarditis without germs or Aschoff's nodules, Osler's erythema in which the cutaneous manifestations resemble purpura, polymorphous erythema, urticaria and angioneurotic edema in which the cutaneous reaction would be toxic and secondary to a septicemia during an amicrobic phase, the Senear-Usher syndrome which is characterized by the concomitance of lupus erythematosus of face and scalp, phlyctenae analogous to pemphigus at the level of thorax and limbs, scaly and seborrheic plaques of the type of Hebra's congestive seborrhea around the former lesions, and residual pigment plaques in regressing lesions which is considered as intermediary between pemphigus and acute lupus erythematosus, chilblain lupus which is characterized by lupus erythematosus of the face together with papulonecrotic tuberculids of the limbs in young individuals with acrocyanosis, frequent relapses, and systemic lesions, Lian's malignant lupo-erythemato-visceritis which is described as a systemic infectious disease coinciding with lupus erythematosus with a typhoid-like syndrome, multiple visceral and serosal manifestations of an acute galloping course with or without remissions but with a fatal outcome, and the syndrome of Keefer and Felty which is almost always fatal. Perhaps many of these syndromes correspond to the same disease entity and a synthesis would be preferable to description of additional syndromes.

After a survey of the cases reported in the Spanish literature the author reports his own case which concerned a woman aged 28, who first developed an ulcer of the nasal mucosa one year before admission. Treatment with various ointments had been unsuccessful and after two or three months, high fever of 8 to 10 days' duration had supervened. During this febrile period additional ulcers had appeared at the level of the lips and the skin developed an inflammation which resembled and which was diagnosed as erysipelas. Sulfonamide treatment was instituted but had to be discontinued because of intolerance and aggravation of the con-

dition. After the high fever subsided slight temperature elevations persisted and the nasal inflammation subsided, but not completely as some spots persisted and extended to the cheeks. After six months another more intense attack occurred and lasted about two weeks; the facial lesions extended and new ones appeared at the level of the hands.

The family history was noncontributory. The personal history included measles and some articular pains, particularly at the level of the ankles which on some occasions were inflamed; there was also a history of frequent bronchial catarrhs.

On admission, the nose, the upper lip and almost the entire cheeks showed a purple color, congestion and edema, and there was follicular hyperkeratosis and some adherent unctuous scabs, detachment of which revealed the typical spurs of lupus erythematosus and also small hemorrhages. The palmar surfaces of all 10 fingers showed punctiform hyperkeratotic lesions which were not tender, a purple coloration and marginal scales. There were some slight adenopathies of difficult interpretation. The joints were painful on slight pressure. The chest organs appeared normal. Liver and spleen were not palpable. The serologic reactions were negative. The blood picture showed 4,030,000 erythrocytes and 3,800 leukocytes with a differential count of 1 eosinophilic cell, 1 juvenile neutrophilic cell, 2 staff cells, 60 segmented cells, 28 lymphocytes and 8 monocytes. The sedimentation rate was 127 and 133 mm. after one and two hours respectively. The urinalysis showed slight traces of albumin but no other abnormalities; the sediment was normal. The chest plate was negative. Mendel's test was negative.

Sulfapyridine treatment was instituted but could not be followed up as the patient returned to her village. After three days the process became reactivated, with fever around 40° C. for a period of 10 days; pleuropulmonary symptoms supervened but no signs of tuberculosis were demonstrable. The blood culture was also negative. The patient's course was downhill, prostration and malaise became more severe and she succumbed.

Acute lupus erythematosus, periarteritis nodosa and acute rheumatic fever have a similar pathologic basis. Periarteritis nodosa may be the final result of an anaphylactic reaction from hypersensitivity, in analogy to acute rheumatic fever and acute lupus erythematosus. The offending antigens may be variegated and their identification is difficult; more than one antigen may be acting in the same patient. These antigens may be nonbacterial and may include some not considered pathogenic at present.

The author considers it interesting to classify the varieties of lupus erythematosus and the various syndromes described above, either involving the skin exclusively or the peripheral circulation diffusely, but from the practical point of view he considers it more important to pay attention to the extension of the process in the capillary system and above all to investigate the etiology. Antibiotics and sulfonamides are ineffective and may sometimes be dangerous as they may aggravate the leukopenia. A filtrable virus may be the common etiologic factor. Any of the manifestations of the capillary system should induce the attending physician to a more complete exploration of the system, and it will always be interesting to know the elemental cutaneous lesions which in the grave malignant type of this affection are localized in the face, and also at the level of the fingers.

Dicumarol Fatality in Severe Hypertensive and Arteriosclerotic Cardiovascular Disease Despite Controlled Therapeutic Level — London, Rose E. — *Circulation*, 1: 1205 (May) 1950.

"The following case of dicumarol fatality is presented for two reasons. First, it illustrates the disastrous complications of the drug in spite of control at recommended therapeutic levels in an elderly patient with severe hypertensive and arteriosclerotic cardiovascular disease. The method of prothrombin time determination in this case was the standard Quick method for which the therapeutic level of 30 to 50 seconds is considered desirable and safe. Second, it serves to emphasize the danger of a false sense of security in patients treated with a dangerous drug over a long period of time. In this case the patient had been controlled on similar dosage for

a period of seven months without serious complications.

"Case Report.—Mrs. D. T., a 70 year old white woman, was seen for the first time January 28, 1949, complaining of palpitations. She had always been in good health, had four normal pregnancies, and led a strenuous life of work until 25 years ago when she was discovered to have hypertension, which remained 'above 190' on repeated examinations. For 19 years she had frequent attacks of rapid heart action and weakness and had been receiving digitalis over the past 14 years for shortness of breath and fatigue. Four years ago an encapsulated carcinoma of the right breast was enucleated.

"In July 1948 the patient had an attack of weakness in the left arm and leg associated with stupor. During hospitalization in another city, dicumarol therapy was started for the first time and was given continuously in constant dosage of 50 and 100 mg. on alternate days. Prothrombin time was said to be well maintained, except on one occasion when transient hematuria appeared. She continued on the same dosage of dicumarol for about one month after she had left the care of her previous physician.

"At her first visit on January 28, 1949, the patient complained of palpitations during the preceding 12 hours, without dyspnea or chest pain. Physical examination revealed a well preserved, alert, 70 year old woman in no acute distress, not dyspneic or cyanotic. Examination of the head and neck revealed no abnormality except for the fundi which showed irregularity and tortuosity of the vessels with normal disks. There was a small scar on the right breast, but no masses were felt in either breasts or axillas. The lungs were clear to percussion and auscultation. The heart was moderately enlarged with the point of maximal impulse in the sixth intercostal space, outside the midclavicular line. The sounds were of fair quality. There was a totally irregular rhythm with a ventricular rate of 120 and a pulse rate of 100. A rough systolic murmur was heard over the base, but no thrills were present. The blood pressure was 220/120.

"Abdominal examination showed no abnormality. Neurologic examination revealed equal strength in both arms and legs but a slight lag in rapid, rhythmic, alternating movements of the left hand and increase in tendon reflexes of the left biceps, triceps, knee, and ankle. A positive finger-stretch reflex was present in the left thumb, and the abdominal reflexes were absent bilaterally. Cranial and sensory nerves were intact. The extremities showed no edema.

"Fluoroscopy of the chest revealed normal movement of the diaphragm and slight increase in pulmonary markings. The roentgenograms revealed a generalized increase in pulmonary markings and a generalized increase in the size of the heart with blunting of the apex and enlargement of the left ventricle. The aorta was markedly elongated, widened, calcified, and tortuous.

"The hemoglobin was 15.5 Gm. (92 per cent) and the white blood cells numbered 7,750. Urine was normal except for a 1+ albumin reaction.

"The rapid heart rate and pulse deficit subsided satisfactorily with increase in the dose of digitoxin and the patient was advised to discontinue taking dicumarol since she refused adequate laboratory follow-up. However, one month later, the patient's previous physician visited her and on February 29, 1949, again started her on the same dosage of dicumarol as employed on prior treatment. Her prothrombin time on March 8, 1949, was 70 per cent of normal or 20 seconds (normal 16 seconds) on alternate doses of 50 and 100 mg. daily. Her dose was increased to 100 mg. a day, and one week later the prothrombin time was 38 per cent normal or 42 seconds. It was felt that, in her case, less than the usual therapeutic level might be safer and therefore, on March 15, 1949, she was returned to her previous dosage. The following week she did not appear for her weekly prothrombin test, but on March 28, 1949, she returned, complaining of vague discomfort in the epigastrium, associated with anorexia and frequency of urination of 48 hours' duration. Physical examination revealed no change from the previous conditions, but a urinalysis showed 10 to 20 red blood cells and 2 to 5 white blood cells per high power field. Dicumarol was therefore permanently discontinued.

"On the following day, March 29, the patient developed increasingly severe precordial pain. A half hour later she was

found to be in extreme pain, acutely ill, pale, cyanotic, and sweating. Over the following 15 minutes the blood pressure dropped from 220/110 to 120/80. There was no sign of cardiac failure. The ventricular rate was 110 and irregular, with a pulse rate of 88. The patient was given oxygen, morphine sulfate, and was hospitalized.

"Her prothrombin time on admission was 40 seconds (control 13 seconds) and on the following day the nonprotein nitrogen was 53 mg. per 100 cc. of blood and a blood count revealed 4,200,000 erythrocytes with 13 Gm. hemoglobin. The leukocytes numbered 18,200 with 83 per cent segmented polymorphonuclear cells (5 stab and 1 juvenile form) and 11 per cent lymphocytes. The Kahn reaction was negative. Urinalysis showed 4+ albumin reaction and 8 to 10 white blood cells and 30 to 40 red blood cells per high power field. On the following day there was 3+ albumin reaction and 40 to 50 white blood cells with 15 to 20 red blood cells per high power field and a moderate number of hyaline and granular casts. The electrocardiogram showed auricular fibrillation, left axis deviation, and depression of the RS-T segments in all limbs and chest leads consistent with digitalis effect. There was no evidence of acute myocardial infarction.

"Over the following 12 hours the patient gradually lapsed into deep coma. Her blood pressure varied from 80/60 to 120/80 and there was no evidence of cardiac failure. Her urinary output over 36 hours was 30 cc. and the nonprotein nitrogen on the third day arose to 83 mg. per 100 cc. of blood. Generalized hypotonicity appeared and there were no localizing signs or involuntary movements. There was no evidence of bleeding from the external orifices, although large ecchymoses surrounded the areas of venipuncture. The patient exhibited intermittent Cheyne-Stokes respiration, gradual rise in temperature, and finally expired on April 1, 1949, 74 hours after admission.

"Postmortem Examination: Gross Findings. External examination revealed the well nourished body of an elderly white woman with a few ecchymotic areas over the dorsum of the hand and the antecubital fossae, surrounding points of venipuncture. There was no cyanosis, jaundice, or petechial hemorrhages.

"Scattered through the root of the mesentery one noticed small hematomas, varying in size from 0.5 cm. to several centimeters in diameter. The peritoneal surfaces were smooth and glistening. The liver and gallbladder were normal. In the tissues surrounding the pancreas was noted a rather diffuse hematoma, which also extended to the pararenal and adrenal areas on both sides. The parenchyma of the adrenals, however, was grossly normal. The mucosa of the gastrointestinal tract was normal throughout.

"The capsule of the kidney stripped with ease revealing a roughly granular cortex with loss of normal corticomedullary demarcations. There were a few 0.5-cc. cystic areas noted within the cortex. The pelves, ureters, and bladder were grossly normal.

"The chest was bilaterally symmetrical. The pleural surfaces of the lungs were smooth and glistening. The right pleural cavity contained no free fluid. The left pleural cavity contained a few centimeters of blood-tinged fluid, and at the hilar area of the left lung there was a blackish red grapefruit-sized mass that lay subpleurally but not in the mediastinum. This mass was found to be a large blood clot, the origin of which was undeterminable since there was no break in the continuity of the adjacent blood vessels; and it was therefore judged to be a hemorrhagic diapedesis. Cut section of the left lung showed a hemorrhage within the parenchyma itself situated approximately 3 or 4 finger-breadths from the hilar region.

"The heart was enlarged, and there was rather extensive pericarditis present, fibrinous in type and fairly recent, allowing for easy stripping of the visceral and parietal pericardial layers. The left ventricle was markedly hypertrophied and the papillary muscles of the left ventricle were thickened. There was a slight thickening of all the heart valves. The myocardium showed no gross evidence of fresh infarction although there was distinct scarring of the left ventricle particularly in the anterior part of the apical area and the upper posterior wall. The endocardium of all four chambers, with special reference to that covering the papillary muscles, showed numerous small and large irregularly shaped fresh hemorrhages varying in

size from 0.5 to 1.5 cm. in diameter. Both branches of the left coronary artery showed marked sclerosis and narrowing of their lumens but no thrombosis.

"The ascending and thoracic portions of the aorta were markedly sclerotic with atheromatous deposits throughout, the intimal surfaces of which were intact.

"Microscopic Findings: The areas of hemorrhage described grossly showed tremendous pools of red blood corpuscles in which were floating remnants of walls of the small vessels, precapillaries and capillaries, and pieces of lymphatic tissue and even of cartilaginous tissue. There were no vascular changes seen within the floating remnants of the vascular tree. The wall of the pulmonary vessels showed thickening and hyalinization with pillow-like protrusions formed by splitting of the elastic fibers. The alveoli had collapsed in some areas and were distended in others with very thin interalveolar septums between.

"The muscular layers of the esophagus were surrounded by collections of red blood cells.

"Sections of the four chambers of the heart, the papillary muscles, the valvular apparatus, and the interventricular septum as well as the coronary tree showed that there was a preexisting pathologic state plus a superimposed acute change. The preexisting process consisted of (1) thickening and hyalinization of the mediums of the left coronary tree including the small branches with splitting and rupture of the elastic fibers, with and without deposits of lime salts, and (2) numerous small and large fibrotic scars of the myocardium, especially the left ventricle, and to a minor degree of the anterior part of the interventricular septum. The acute changes consisted of irregularly shaped hemorrhages of varying size located in the pericardium, the endocardium, and within the papillary muscles and the myocardium of the left ventricle. Most of these hemorrhages were fresh and no reaction was noticeable. There was, however, one area where the hemorrhage was beginning to be organized from the periphery.

"The aorta showed heaping up of the intima with cholesterol depositions, with and without calcification. The adventitia showed extensive fresh hemorrhages.

"In the kidneys, there were marked vascular changes in the glomeruli with hyalinization of the loops. Distention of the convoluted tubules with degeneration of the epithelium and increase in the interstitial tissue was present. The arteries as well as the arterioles showed evidence of hyalinization of the mediums with splitting of the elastic fibers.

"In the pericentral areas of the liver the sinusoids were markedly engorged with red blood cells and the adjacent parenchymal cells were compressed and vacuolated. The periportal liver cells were normal.

"In the pancreas the parenchymal cells were well preserved and in rare areas there was infiltration of red blood cells. In the capsule, however, there were many collections of red blood cells and numerous macrophages containing yellow pigment.

"The sinusoidal spaces of the spleen were markedly engorged with red blood cells. Frequently, the splenic architecture was distorted by areas of hemorrhage."

It appears that, even with careful laboratory control over a prolonged period of time, factors of unknown nature may come into play and cause a fatal outcome. "In this case the factor which was believed to be contributory to the widespread hemorrhage was the presence of severe hypertensive and arteriosclerotic cardiovascular disease. While the mechanism of bleeding in dicumarol poisoning is unknown and while severe hypertensive and arteriosclerotic cardiovascular disease does not primarily manifest itself by bleeding, it is supposed that in some way the presence of severe hypertension and arteriosclerosis impairs the endothelial continuity of the vascular tree with resultant increased diapedesis when dicumarol is present. The risk attending the administration of dicumarol in such a case is therefore so great that it behooves the physician to weigh carefully the indications for its use, even when accurate control is assured."

Pediatrics

Observations on the Development of Rheumatic Fever and Glomerulonephritis in Cases of Scarlet Fever Treated with Penicillin — WEINSTEIN, LOUIS, BACHRACH, LOUIS AND BOYER, NORMAN H. — *New England Journal of Medicine*, 242: 1002 (June 29) 1950.

"That rheumatic fever and glomerulonephritis are preceded in most cases by infection of the upper respiratory tract with the beta-hemolytic streptococcus is generally accepted by most students of the two diseases. Because of this close association it appears possible, on theoretical grounds, to eliminate either or both of these late streptococcal complications by early eradication of the causative organisms during the acute phase of infection. It was for this purpose that the investigations reported below were carried out; patients with scarlet fever were treated with penicillin, and the incidence of rheumatic fever and glomerulonephritis determined. In the cases in which these diseases occurred careful detailed investigations of the clinical and laboratory features were made."

"The occurrence of glomerulonephritis as a late complication of scarlet fever has been known for many years; careful study reveals an incidence of about 1 or 2 per cent of this renal sequel in untreated streptococcal pharyngitis. The clinical picture is usually very variable; in some cases only the laboratory features of the disease such as hematuria, albuminuria and cylindruria are present, whereas others may show rarely the complete syndrome of urinary abnormalities, azotemia, hypertension, oliguria progressing to anuria, convulsions, uremia and death. Most cases lie between these two extremes. Many patients with scarlet fever, especially those with severe rashes, have albuminuria and hematuria early in the course of the illness; these are probably due to fever and the action of the erythrogenic toxin on the kidney and are not related to glomerulonephritis. This diagnosis can be made only if a 'latent' period of at least two weeks between the onset of the acute streptococcal infection and the appearance of abnormal constituents in the urine, with or without clinical manifestations, is present."

Every patient with scarlet fever admitted to the writers' hospital was treated with penicillin if the duration of the rash was less than 48 hours and no antibacterial therapy had been given prior to admission.

"The penicillin given to all the patients was the crystalline G preparation. Two regimens of therapy were used; most patients received 15,000 units dissolved in physiologic saline solution every three hours for 10 days; a smaller group was given 100,000 units of antibiotic (in a tablet containing calcium carbonate as buffer) orally every 3 hours for 10 days. Blood levels were not determined."

"A total of 167 patients were included in this study; of these, 127 received penicillin by the intramuscular route; the others were given the antibiotic orally. One hundred and fifty were between the ages of 2 and 15 years; 126 were less than 10 years old. This represents a good sampling with respect to age since most were in the group in which the incidence of rheumatic fever and glomerulonephritis is highest after infection with the beta-hemolytic streptococcus.

"Cases of Rheumatic Fever.—Twelve patients of the entire group with scarlet fever who received penicillin (2 orally and 10 intramuscularly) had laboratory or clinical manifestations, or both, highly suggestive of acute rheumatic fever. Beta-hemolytic streptococcus (group A) was isolated in all cases."

"Four patients were between 3 and 5 years of age, and 7 were between 6 and 16; 1 was 31 years old."

"One of the most important factors influencing the occurrence of rheumatic fever after the penicillin treatment of streptococcal infection may be the duration of the interval between the onset of clinical manifestations and the first exhibition of chemotherapy. . . . In the present study sore throat was present in 93 of the entire group for 24 hours or less before ther-

apy was instituted, and in 120 the interval was 48 hours or less. In the patients in whom rheumatic fever appeared, pharyngitis had been noted for one day or less in 7, for two days in 4 and for four days in 1. It is apparent, therefore, that about 72 per cent of the entire group and 91 per cent of those in whom rheumatic fever subsequently developed had had clinical streptococcal disease for 48 hours or less before treatment with penicillin was instituted."

"All the patients in whom rheumatic fever later appeared had a so-called 'latent period,' the average duration of which was nine and two-tenths days."

"Only 5 of the 12 patients showed an appreciable rise in temperature during the period when clinical and laboratory changes suggestive of acute rheumatic fever were most evident. It is striking, indeed, that in the other 7 cases there was complete lack of a febrile response at times when arthralgias were present, new murmurs were appearing and the electrocardiogram was showing progressive changes. In 1 child who had signs of aortic regurgitation (present on reexamination six months after onset) without any electrocardiographic abnormality the entire episode was completely afebrile."

"Subjective or objective involvement of the joints is one of the major criteria for the diagnosis of rheumatic fever." The authors' experience with first attacks of this disease in children in whom streptococcal pharyngitis was not treated with specific antibacterial agents has impressed them, however, that migrating polyarthritis is uncommon and that migratory or nonmigratory polyarthralgia or, frequently, monarthralgia of quite short duration is much more frequent. Thus, in the days before penicillin treatment, they observed a young patient with an afebrile monarthralgia of one wrist of 12 hours' duration in whom congestive heart failure developed four weeks later and who after three years had mitral stenosis. "Little significance can be attached to joint pains in the acute phase of scarlet fever so far as rheumatic fever is concerned, since arthralgia is not uncommon early in streptococcal infections, especially if the disease is severe. The latent period assumes great importance here. In the group of cases reported in this paper a total of 30 patients had arthralgia; in 18 it occurred during the first six days after the onset of pharyngitis and had, therefore, no probable relation to rheumatic fever. In the other 12, the joint manifestations did not appear until at least nine days after the onset of sore throat. Only 4 of these were classified as having rheumatic fever since they were the only ones who had additional evidence of this disease; all showed electrocardiographic abnormalities, and 2 had persistent cardiac murmurs that had not been present during the first week of hospital observation."

"Four patients who had no abnormal heart sounds or only 'functional' ones at the time of admission to the hospital later manifested what were interpreted as 'organic' cardiac murmurs during the period of observation. In 2 cases arthralgia was present; in 3, in which persistent signs of mitral insufficiency appeared, there were also electrocardiographic changes. The fourth patient was treated with penicillin within 24 hours of the onset of streptococcal pharyngitis but still showed signs of aortic insufficiency, which persisted; he had no abnormal electrocardiographic findings at any time. In 1 of the cases in which a mitral systolic murmur was first noted in the hospital, clinical evidence of mitral stenosis was present nine months after the diagnosis of rheumatic fever was first made."

"Since electrocardiography may be of value in the diagnosis of rheumatic fever, it is essential to define the changes that are to be considered significant. It is common practice in reporting mass surveys to list all findings such as premature beats, shifting pacemaker, auriculoventricular nodal rhythm or other wholly normal variations, with the implication that they indicate cardiac involvement. In the present study all such deviations from the usual were considered insignificant. A few other more unusual departures from the normal pattern were also disregarded, provided they were stable during the entire period of observation and were present at the time of initial hospitalization. One patient, 8 years old, consistently showed prominent S waves in all leads, with increased duration of the QRS complex to 0.09 second. Another had an even more unusual pattern, with prominent Q waves in the standard

limb leads and in lead CF_4. Neither of these children showed other evidence of heart disease or rheumatic fever. In 2 cases intermittent coronary sinus rhythm was present, but no significance was attached to it. There appears to be little difference of opinion concerning the frequency and importance of the development of auriculoventricular block as a manifestation of rheumatic activity; it makes little practical difference whether the cause of the disturbance is local or vagal. The principles and rules adopted for the diagnosis of prolongation of the PR interval are of great importance. . . . PR intervals exceeding the predicted upper limit of normal for age and rate by only 0.01 second were considered normal, those from 0.01 to 0.02 second borderline, those over 0.02 second probably abnormal, and those of 0.04 second or longer as definitely pathologic. Certain qualifications, however, limit the value of these arbitrary standards. Intervals that are unvaryingly prolonged in serial records throughout the period of observation must be viewed dubiously; these may represent an occasional normal variation, or may be due to a congenital conduction defect or to a residual scar from previous inflammatory processes. PR intervals showing noteworthy variation from day to day are much more reliable. In this connection it seems worth emphasizing that a PR interval that increases, even a little, with a rise in rate may be an important finding—for example, a prolongation of only 0.02 second with an increase of 30 beats per minute. Normally the PR interval shortens with increasing rate, whereas the reverse would be expected if a process tending to interfere with recovery of the conduction tissue was present. Change in the position of the pacemaker as a cause of such variation with alterations in the heart rate must be kept in mind, however. This was observed in 2 patients; the PR interval in both cases was about 0.13 second, with a cardiac rate of from 50 to 60 per minute, and 0.16 second or slightly longer when the pulse was 90 to 100. The form of the P waves, however, was quite different in the two records. Careful study of the contour of the P waves will therefore eliminate this type of error.

"Eleven patients of the 167 studied showed electrocardiographic abnormalities. Ten had significantly increased auriculoventricular conduction time. The PR interval was longest, 0.22 second, in a 17 year old patient; in 6 cases it was 0.20 second or more, and in the remaining 4 the maximum values were 0.19, 0.18, 0.18 and 0.19 second at the ages of 8, 3, 4 and 4 years, respectively. . . . Variation in conduction rather than a single value was considered significant. For example, an 8 year old child had a PR interval of 0.14 second at a heart rate of 94 six days after the onset of scarlet fever. On the thirteenth day the rate was 88 per minute, but the interval had increased to 0.19 second. The latter value is only 0.02 second more than the upper limit of normal and, so, is no more than borderline; the increase of 0.05 second without change in cardiac rate, however, is undoubtedly significant.

"Prolongation of the QT interval is a reliable and nearly constant finding in the carditis of rheumatic fever. The same principles are involved in the evaluation of the significance of changes in this measurement as are concerned in the determination of the importance of alterations in the PR interval. With 1 exception, all the patients in this study who had prolonged PR intervals at one time or another also had elongation of the QT interval, but not always in the same record. In addition, 1 patient exhibited definite lengthening of the QT interval without any evidence of increase in auriculoventricular conduction. Prolongation of the QT interval was not extreme in any case, the maximum being 0.04 second more than the upper limit of normal. In 7 cases there was at least 1 record with a QT interval longer than the upper limit of normal, whereas in 3 the actual value never exceeded normal; in all, however, there were serial changes of as long as 0.06 second, at comparable heart rates. For example, a boy with a cardiac rate of 91 on the fifth day of illness showed a PR interval of 0.16 and a QT interval of 0.28 second; on the eighth day the rate was 91 and the PR interval was still 0.16 second, but the QT interval increased to 0.34 second—a rise of 0.06 second. The PR interval did not increase until the thirteenth day in this case.

"Changes in the ST segment and the T waves were not encountered in this series of rheumatic subjects, although 2 patients with acute glomerulonephritis showed flattening or inversion of the T waves in leads 1 and 2. During the acute stage of scarlet fever there was slight to moderate depression of the ST segment and lowering of T waves in many cases; this was attributed to the tachycardia and fever. These early changes differed in no way in patients whose course was uncomplicated and in those who later had evident rheumatic fever. They are entirely nonspecific and occur with any type of infection associated with rapid heart rate and fever. The unmistakable pattern of pericarditis did not occur in this series.

"Because there has been considerable discussion and controversy concerning T wave changes, and since their evaluation is a great deal more subjective than measurement of the PR or QT interval, a preliminary study was made of the ventricular gradient in a group of 41 patients with established rheumatic fever not included in this paper. It was hoped that such an approach to the problem would place the evaluation of T wave changes on a more objective basis. This did not prove to be the case, for the direction and magnitude of the gradient showed no abnormalities. This is not to say that departures from normal may not be found in some cases, but the fact that they were not encountered in 41 cases of active rheumatic fever selected on the basis of the presence of prolonged PR intervals renders the method unsuitable for routine use. It is noteworthy, however, that none of the group in which the gradient was investigated showed what were considered to be significant T wave changes empirically, although some T wave alterations were present that might have been considered important by other observers.

"Unfortunately, because of the magnitude of the study, it was impractical to take multiple precordial leads, only lead CF_4 being used. It was impossible, therefore, to attribute significance to changes in the T wave in the chest lead when this was an isolated finding. Changes in the contour of the QRS complex from one record to another indicated clearly that the position of the electrode was not constant. Even when the QRS complex remained essentially unchanged it was not thought safe to attribute significance to T wave changes, inasmuch as the two components of the ventricular complex may vary independently with variations in placement of the electrode. There seems to be no doubt that study of the precordial T wave would have yielded helpful information if multiple chest leads had been employed."

"Four patients showed return of beta-hemolytic streptococci to the respiratory tract after having been free of them for varying periods. In no case did pharyngitis recur, however. In all cases the bacteriologic relapse occurred after penicillin therapy had been stopped, and in 3 it was noted after clinical and laboratory evidence of rheumatic fever was already present. The incidence of recurrence of positive cultures in patients with rheumatic fever was almost identical with that observed in the entire group of those with scarlet fever given penicillin—about 33 per cent. . . . This was due not to failure of the antibacterial therapy but to contamination of treated patients by association with persons with fresh, acute streptococcal infections or by contact with medical and nursing personnel who were temporary carriers of the streptococcus. The data obtained in this study do not indicate any relation between bacteriologic relapses or recurrent streptococcal pharyngitis and the development of rheumatic fever."

"In only 1 case was the erythrocyte sedimentation rate elevated at a time when rheumatic activity was thought to be present. In 8 others it remained entirely within normal limits, whereas in 3 it fell from abnormal to normal heights while electrocardiographic changes were still in progress."

"None of the cases studied developed any detectable precipitin for the nucleoprotein M of the serologic type of streptococcus with which they were infected. Only 4 patients had a rise in antistreptolysin titer during the period of illness and follow-up study, and only 2 showed an increase in antistreptokinase activity to levels above normal. In only 1 case was both the antistreptokinase and antistreptolysin content of the serum elevated."

"The following signs and symptoms suggestive but not diagnostic of rheumatic fever appeared in the patients with scarlet fever during the period of hospitalization: All followed a latent period of at least 10 days; periumbilical pain of three to five days' duration occurred in 4; arthralgia involving more than one joint and continuing for at least two days without electrocardiographic changes at any time appeared in 4; and repeated epistaxes lasting a minimum of three days were present in 4. No new cases of rheumatic fever were detected after the usual three weeks of hospitalization. A number of patients, however, had clinical manifestations in the first month after discharge that raised the suspicion of the presence of the rheumatic state. Thus, 8 had monarthralgia or polyarthralgia, 6 had recurrent epistaxes, and in 11 there were bouts of abdominal pain. No new murmurs appeared in any case, and repeated electrocardiograms were consistently within normal limits. The significance of these 'minor' manifestations in the absence of any of the 'major' ones after an established streptococcal infection is difficult to evaluate in terms of a specific diagnosis of rheumatic fever. Those experienced with this disease have been impressed, however, with the occasional case in which only 'minor' signs and symptoms are present and in which there is evidence of rheumatic heart disease later in life."

The combination of a proved streptococcal pharyngitis, a latent period, joint pains and electrocardiographic changes provides a set of circumstances that to the authors' mind constitutes the syndrome of acute rheumatic fever. "There were 4 patients in this group who showed such manifestations, 2 of whom developed new cardiac murmurs; in addition, there were 2 others who subsequently had evidence of valvular disease." If only these 6 cases are considered as proved rheumatic fever, the incidence of this poststreptococcal sequel is still 3.6 per cent in this series.

"Cases of Glomerulonephritis.—Six patients of the group with scarlet fever who were treated early in the acute phase of their infection with penicillin showed clinical or laboratory evidence, or both, of acute diffuse glomerulonephritis as a late complication."

"The patients ranged in age from 3 to 36 years; 2 were 3, 2 were 6, 1 was 15, and the last was 36 years of age."

"In 4 cases penicillin was given within 24 hours of the first manifestations of streptococcal pharyngitis, and in 2 others treatment was not instituted until sore throat had been present for about 48 hours. Thus, two thirds of the patients who subsequently had glomerulonephritis were treated for the initiating streptococcal infection within 24 hours of the time when it first became clinically apparent."

"Many persons with severe scarlet fever may show albuminuria, cylindruria and varying degrees of hematuria in the first week of the disease; these urinary abnormalities are undoubtedly due to the combined effects of fever and the action of the erythrogenic toxin on the renal glomerular capillary. It is very important, therefore, to insist on a 'latent' period—during which there are no abnormal constituents in the urine—of at least 10 to 12 days before the diagnosis of acute diffuse glomerulonephritis is considered seriously. With this as a criterion, none of the patients in this study showed any manifestations suggesting an important renal complication until 18 to 25 days after the onset of streptococcal pharyngitis."

"Only 3 patients showed any febrile response during the period when manifestations of glomerulonephritis were most evident; in no case did the temperature rise over 102° F. by rectum. In the remaining 3 cases the entire course of the renal disease was characterized by the absence of fever."

"The diagnosis of glomerulonephritis was not made in the absence of any of the characteristic urinary abnormalities. Thus, all the patients showed, after a 'latent' period, varying degrees of albuminuria, cylindruria and hematuria. As is seen in this form of Bright's disease, the quantity of abnormal constituents in the urine varied from time to time. The shortest duration of the disease was 4, and the longest 28 days. No case of subacute or chronic nephritis was observed in this study."

"Only 1 patient had clinical evidence of glomerulonephritis; this was a 36 year old man in whom moderate azotemia, acidosis, hypertension and oliguria, in addition to

cylindruria, albuminuria and hematuria, developed. Nitrogen retention and decreased urinary output persisted for about two weeks, hypertension was present until the fourth week, and the urinary abnormalities disappeared about 28 days after their first appearance. The relative absence of clinical evidence of renal disease in most of these patients reemphasizes the need for frequent examinations of the urine in the third to the sixth week after the onset of a streptococcal pharyngitis. Glomerulonephritis characterized only by the presence of abnormal constituents in the urine has also been observed in cases of scarlet fever not treated with penicillin. Failure to examine the urine at frequent intervals for several weeks after an acute episode of streptococcicosis will cause these relatively mild nephritides to be missed completely. It may be such incidents that account for the cases of chronic glomerulonephritis discovered first in adult life without a history of an acute attack of this form of Bright's disease."

"Three of the patients who had glomerulonephritis revealed elevation of the erythrocyte sedimentation rate during the course of this complication. In the others the sedimentation rate remained normal in spite of the presence of cylindruria, hematuria and albuminuria."

"In no case of nephritis was there evidence of a secondary streptococcal infection prior to the onset of renal disease. In 3 cases bacteriologic relapse was noted. . . . As in rheumatic fever, there appeared to be no relation between the recurrence of positive cultures in the nose or throat (or both) and the development of the renal complication. No case of persistence of streptococci in the respiratory tract during or after penicillin therapy was noted."

"None of the patients in this group developed any precipitin in their serum against the M nucleoprotein of the serologic type of beta-hemolytic streptococcus isolated from the respiratory tract during the acute phase of scarlet fever. Not a single case of glomerulonephritis showed any rise in antistreptolysin or antistreptokinase titer; this is quite striking in view of the association of high levels of these antibodies with this form of Bright's disease that is often cited."

Chloromycetin in Salmonellosis — Quintanilla Ulla, Jaime—*Medicina*, 18: 356 (May) 1950.

The therapeutic problem of salmonellosis has been solved with chloromycetin, the older treatments having proved disappointing. Chloromycetin treatment leads to rapid detoxification of the patient and rapid defervescence and to a great reduction of the incidence of complications like perforation and hemorrhage. The author's own material included 5 cases of paratyphoid B and 1 of typhoid fever; in all cases the results were dramatic, particularly in the case of typhoid fever which showed characteristics of great malignancy. The author was unable to use the dosage recommended by American authors due to scarcity and high price of the drug, and he is of the opinion that in many cases there is no necessity to use the drug.

The most interesting case was that of typhoid fever, it concerned a girl aged 6, with a history of anorexia and frequent attacks of acetonemia. The girl was seen on the first day of her affection; while in preceding attacks she had shown only very slight subfebrile temperature elevations, this time she showed a temperature of 39.2° C. and intense obnubilation. The urine was intensely positive for acetone and urobilin and slightly positive for urobilinogen. The usual treatment of glucose enemas had proved ineffective this time. The girl was in a semicomatose condition and responded only with difficulty to questions. Auscultation was negative. The tonsils were reddened; the tongue was strawberry red and intensely coated. Acetone odor was noticeable in the entire room. In the evening roseola appeared at the level of the upper abdomen. The arterial pressure was 85/50 mm. An ampule of 5 mg. of cortical hormone was injected. Aminopyrine was given rectally and 2 ampules of 500 mg. of vitamin C were injected daily. Fever and obnubilation persisted for two days, the roseola increased in number, and the entire mouth was invaded by aphthae. On the third day a positive blood culture for typhoid fever bacilli was obtained. On the fourth day the blood picture showed 4 million erythrocytes and 6,400 leukocytes with 19 per cent staff cells, 60 per cent segmented cells, 19 per cent

lymphocytes and 2 per cent monocytes. The urine contained acetone and urobilin and gave a frankly positive Ehrlich's diazo reaction. On this day chloromycetin was finally obtained; the first dose of 1 Gm. was given, and then 0.25 Gm. was given every three hours up to a total of 9 Gm. The vomiting subsided, the sensorium cleared up rapidly, mouth and tongue became normal rapidly, and the temperature fell, reaching a normal level within four days. Eight days after onset the patient was subjectively cured. Blood culture and agglutination tests were negative. The urine still gave a positive Ehrlich's diazo reaction but no longer contained acetone and bile pigments. The leukocytes numbered 5,000, with 3 per cent staff cells, 33 per cent segmented cells, 61 per cent lymphocytes and 3 per cent monocytes. The negative agglutination test in spite of the positive blood culture on the fourth day is explained by the fact that the bacteriostatic activity of the antibiotic, by diminishing the septicemia, impeded formation of antibodies in the reticuloendothelial system due to the lack of stimulus. The patient recovered her appetite and gained weight. Cure was obtained within a much shorter period of time than with any earlier treatment.

Excellent results were also obtained in the 5 cases of paratyphoid B. The dosage was not higher than 9 Gm. in any case as no more of the antibiotic was available, and this dosage proved sufficient.

Congenital Thrombocytopenic Purpura. Purpura Haemorrhagica in Pregnancy and in the Newborn — EPSTEIN, ROBERT D., LOZNER, EUGENE L., COBBEY, THEODORE S., JR. AND DAVIDSON, CHARLES S. — *American Journal of Medicine*, 9: 44 (July) 1950.

"During the past 10 years the authors have followed 5 patients with purpura haemorrhagica through 7 pregnancies."

"In all instances the mothers suffered from typical purpura haemorrhagica. The age of onset of the purpura varied from 3 to 28 years; in the last instance the first symptoms of purpura preceded pregnancy by only a few months. In all of the patients the platelet counts were low. The bleeding times were generally prolonged, the clot retractions poor and the tourniquet tests positive. With the exception of purpuric phenomena the patients' past histories were unimportant. In none was there a previous family history of purpura.

"Three of the patients had their spleens removed with at least a temporary rise of the blood platelet count to normal or above and disappearance of the purpura. Splenectomy was performed in 1 patient during the sixth month of pregnancy because of severe epistaxis. The postoperative course was uncomplicated, the epistaxis ceased and the blood platelet count rose to normal. Following splenectomy 2 of the patients have maintained normal platelet counts and have not had purpura for periods of two and three years, respectively. The interval since splenectomy has been 13 years for the other patient and she has had recurrence of thrombocytopenia and of purpura.

"During the period of study 7 children were born to this group of 5 women. Three were females and 4 were males. Six had blood platelet counts below 100,000 per cu. mm. at or shortly after birth. Purpura, generally mild, but with severe melena in 1 instance, was observed in 5 of the children. It was not always possible to follow the blood platelet counts of the infants at regular intervals, but in all instances the platelet counts became normal within 2 years, in 5 within 2 to 4 months after birth. Purpura likewise disappeared. There were no other abnormalities observed in the children at birth and subsequently all developed normally.

"Even though there were few platelets circulating in the blood of most of these children they had few hemorrhagic episodes and none required transfusion therapy. Thrombocytopenia occurred in the children irrespective of their sex and whether they were fed at breast or by bottle. There was no relationship of the age, parity or presence or absence of the maternal spleen to the syndrome in the child. There was, however, a rough correlation between the severity of the disease in the mother and in the child." For example, 2 patients whose symptoms were severe clinically, bore children who had thrombocytopenia for a longer period of time and had more of a hemorrhagic diathesis than the children of 2 patients whose symptoms were of moderate severity.

"In none of the 3 mothers in whom purpura haemorrhagica was known before pregnancy were the purpuric manifestations accentuated by the pregnancies. None experienced complications during labor, at delivery or in the puerperium." Two of these individuals, at times when their platelets were diminished, were subjected to major surgical procedures without the occurrence of abnormal bleeding. An episiotomy was performed on a third without unusual bleeding or retardation of healing.

A review was made of the literature of pregnancies complicated by purpura haemorrhagica. Reports of 39 such pregnancies were found and 7 similar ones have been described by the authors. "In the total group of 46 pregnancies the over-all maternal mortality was 8.7 per cent, while that of the child was 26.1 per cent. One half of the children born living had congenital thrombocytopenic purpura. Within a few months their platelet counts increased to normal and almost invariably remained elevated. No correlation was found between the age, parity, manner of feeding the infant, presence or absence of the spleen in the mother and the syndrome in the child." Congenital thrombocytopenic purpura might be the result of the transfer of an immune body, hormone or other substance across the placental membrane which depresses platelet formation in the infant. "The presence of this substance was quite independent of the presence or absence of the spleen in the mother."

Otitis Media of the Newborn and Its Relations to Occult Mastoiditis with Toxic Nutritional Disturbances, and Purulent Meningitis in the Newborn — Esch, P. — *Geburtshilfe und Frauenheilkunde*, 10: 254 (April) 1950.

Certain anatomic peculiarities of the auditory organ of the newborn have a great significance for the origin and course of ear diseases. The ear drum is relatively thick and resistant, and instead of the mastoid process a small protuberance is present which consists of diploic bone; of the cavities only the main one, that is the antrum, is present. The middle ear still contains more or less gelatinous embryonal tissue and a little seromucous fluid. The tube is short and wide and sometimes gapes so that the communication between the tympanic cavity and the nasopharynx is particularly readily patent.

Foreign body otitis and purulent otitis media must be distinguished. The nasopharynx of the newborn always contains mucus and frequently components of the amniotic fluid particularly abundant in asphyctic newborns. These contents may be aspirated into the middle ear due to the respiratory pressure variations, and the passage of nasal contents into the middle ear may be favored by the use of tracheal catheters for emptying of the nasopharynx of its mucus. Swallowing and vomiting may also be considered as causes of such aspiration. Depending on the degree of the foreign body irritation the fluid in the tympanic cavity is cloudy and purulent, the mucosa contains round cells, and there are accumulations of leukocytes; this abacterial pus formation is frequent; Aschoff coined the term of foreign body otitis. This harmless foreign body otitis is clinically important as it forms a good terrain for infection and purulent otitis media; the myxomatous tissue in the middle ear also forms a good medium. Infection is also favored by the hyperemia of the mucosa due to the delivery, and sometimes by so-called suffocation hemorrhages. Streptococci, staphylococci, pneumococci and other germs, even gonococci, may be found.

Otitis media is frequently found on autopsies of newborns but earlier studies did not always distinguish between foreign body and purulent otitis media. Otitis media is particularly frequently encountered in premature or debile newborns due to diminished resistance and retarded development of the middle ear, and may easily progress into the mucosa of the antrum. Usually it takes its course without local manifestations, and it is justified to speak of latent otitis media. Otorrhea is rarely observed in newborns, as the thick resistant ear drum prevents perforation, and even when a perforation is present the thick pus may not penetrate or may remain in the deeper portion of the duct. In the absence of further complication, an empyema of the middle ear will persist and will be absorbed inasmuch as the pus will not drain through the wide short tube. The author observed otorrhea in the newborn

only twice during 20 years of clinical practice.

The prognosis of uncomplicated otitis media is absolutely favorable in strong infants and depends on the general condition in debile and premature infants. Prophylaxis is desirable, however, as otitis media may be the point of origin of complications. Introduction of germs with the tracheal catheter should be avoided and infants should be kept in the lateral decubitus when a tendency to vomiting exists. Aspiration is favored by the frequently used procedure of covering both nostrils in order to force the infant to take the nipple. Keeping away sources of infection is of utmost importance. Treatment is hardly indicated; the auditory canal may be cleansed with cotton swabs soaked in hydrogen peroxide.

Occult mastoiditis with toxic nutritional disturbances produces no, or only slight, otoscopically demonstrable phenomena and no mastoid symptoms while the remote symptoms are typically of extreme severity, including violent vomiting often resembling pyloric stenosis, sudden loss of weight and nutritional disturbances rebellious to dietary measures. The temperature varies; hypertonia of the muscles, meningism, convulsions, and dehydration are frequently observed. The diagnosis is made by exclusion of primary nutritional disturbances and of infections of other localizations. The author reports such a case in which bilateral antrotomy was carried out in spite of the absence of ear and mastoid symptoms; inflammatory granulation tissue was found in the right antrum and the immediate postoperative improvement after the condition had seemed hopeless proved the correct diagnosis and surgical indication.

Occult mastoiditis occurs almost exclusively in infants; of a series of 65 cases 26 involved the first two months of life, and the youngest patient was 2 weeks old.

The focus in the antrum may be tolerated without symptoms for two to three weeks before the typical syndrome supervenes, so that the actual onset must be placed near birth in many cases. This illustrates the importance of prophylaxis of otitis media in the newborn. One writer stressed the etiologic importance of grippal otitis. Contrary to another, the author does not believe that an intercurrent infection is indispensable for the appearance of occult mastoiditis. Some authors advised caution in the admission of latent otitis and mastoiditis as similar syndromes may be without them but in the 65 cases mentioned by the author, mastoiditis was regularly found on operation or autopsy. There is general agreement that bilateral antrotomy is indicated when there is a justified suspicion of occult mastoiditis. The intervention is usually carried out in local anesthesia; inflammatory granulation tissue, fluid pus or an empyema is found in the antrum and not infrequently a sometimes very intense destruction of the adjacent bones. The results of treatment are not very favorable, the mortality being high particularly in young infants. However, as a hopeless condition is dealt with and the operation is done as a last resort the results appear in a different light; furthermore, causes of death include late operation, unilateral operation, insufficient radical operation and associated diseases. About half the patients were saved in some series, and whenever the infants survived for at least a few days transitory improvement and immediate cessation of vomiting were observed.

The author finally reports 2 cases of purulent meningitis in newborns. The first case concerned an infant born asphyctically with a weight of 3,320 Gm.; it was resuscitated with tracheal catheter and hydropathic stimulation. During the first four days the infant was restless and on the fifth day repeated clonic convulsions and a slight facial paresis appeared. Spinal puncture showed an elevated pressure and a cloudy fluid containing polynuclear leukocytes, with a positive Nonne reaction. The temperature rose only on the eleventh day and reached 39.8° C.; the convulsions became more frequent and violent and the infant succumbed on the fourteenth day. Autopsy revealed suppurative meningitis, pus in the ventricles and total suppurative destruction of the right middle ear with 3 cc. of pus, perforation of the ear drum without otorrhea, and viscous pus in the inner ear, while the left ear, nose, pharynx and tonsils were normal. A mucous capsulated bacillus resembling the Friedländer group was demonstrated bacteriologically.

The second case concerned an infant weighing 2,200 Gm. which was delivered asphyctically by forceps; resuscitation was carried out. Marked jaundice of the newborn supervened. After its partial disappearance on the seventh day a definite greenish yellow jaundice appeared. In the author's experience such a recurrence of jaundice indicates a severe suppurative infection or syphilis, but the general condition was unimpaired at this time. However, in the evening of the same day the temperature rose to 38.2° C., the infant cried at short intervals, and swelling of the right mandibular and cervical regions supervened. Overnight this swelling extended to the right eye, the temperature was 39° C. in the morning, facial paralysis, apathy and superficial breathing supervened, and at noon the infant succumbed. Autopsy revealed meningitis, particularly basally, and the tympanic cavity was filled with thick pus; the ear drum was intensely reddened and showed a perforation, and the depth of the auditory duct was filled with pus. The bones near the tympanic cavity were friable. A recent phlegmon extended from the right petrous bone in the cellular tissue along the styloid process to the level of the larynx, and the submandibular and parotid glands were edematous. The left ear was normal. The left upper lung lobe showed an infarction, and the spleen showed a soft structureless pulp. Hemolytic streptococci were cultured from the pus in the tympanic cavity, the pulmonary infarction and the spleen.

The first case was one of suppurative cerebrospinal meningitis and the second one of suppurative meningitis followed by septicemia, both originating from suppurative otitis media of the newborn; the infection took place through the facial canal which is usually still dehiscent at this stage of development.

Meningitis in the newborn used to be frequent in homes for foundlings but has become rare; however, it may take its course without characteristic symptoms, and only autopsy may reveal that the debility was actually caused by meningitis.

It is probably no mere coincidence that infants born asphyctically were dealt with in the cases of meningitis and occult mastoiditis, and infants who have suffered obstetric traumas require particularly careful supervision. With respect to early diagnosis, minute swelling of the region of the ear, facial paresis and perhaps spinal puncture should be stressed. Otologic consultation is indicated in all doubtful or suspicious cases.

A Follow-Up Study of Pertussis in Infancy — Byers, Randolph K. and Rizzo, Nicholas D. — *New England Journal of Medicine*, 242: 887 (June 8) 1950.

The present study is a follow-up report of 39 children who were admitted to hospital between the ages of 3 weeks and 2 years because of pertussis, with or without complications, during the 14 year period January 1, 1931, to December 31, 1944. "Of the 39 children studied, 3 appeared to have had cerebral defects prior to their pertussis; 1 had multiple congenital anomalies and was obviously defective prior to pertussis contracted at 18 months; a second was a 3 pound, 10 ounce, premature baby who had had neonatal convulsions, grossly bloody spinal fluid and generalized rigidity prior to pertussis and was therefore excluded from further consideration; and a third had an occipital encephalocele and was obviously defective prior to his whooping cough at 21 months of age. A fourth child had measles with encephalopathy subsequent to that disease three months after the pertussis, and this case was also discarded.

"As far as one could tell, the remaining 35 children appeared to be an average group of infants. Their ages at the onset of pertussis varied from 24 days to 23 months. Of these babies, 23 had uncomplicated whooping cough on admission to the hospital, 8 had complicating pneumonia and 4 had complicating encephalopathy, and of these 1 had both pneumonia and encephalopathy."

All patients ran a course of gradually increasing paroxysmal cough that was diagnostically convincing to the hospital staff. Cultures in the hospital have been extremely unreliable, and white cell counts, unless often repeated, were unreliable.

During the past two years the writers have interviewed personally all but 2 of the 35 relevant patients, and on these 2

they have reports by letter that seem entirely convincing.

"Of this total group, 26 had developed normally and were regarded by their families as competent. Fourteen had reached school age and were doing average work or better in grades appropriate to their ages, and of these, 5 were getting honor grades consistently. One of these children had been given pertussis vaccine at 8 months of age and had had an average attack of pertussis at 19 months. Twelve children were still between 3 and 6 years of age, but their developmental histories were average. Of these, 1 seemed anxious, but came from an unstable home, 1 was said to be stubborn, and 1 other had temper tantrums. As nearly as could be determined, their behavior problems did not seem unusual. These children were all considered to have recovered without sequelae, although there could be a difference of opinion about 1 or 2 of the younger ones.

"Among the children who recovered were 2 originally admitted to the hospital because of frank evidences of encephalopathy complicating the pertussis. In addition, 2 children had periods of loss of consciousness after coughing during their hospital stay, and 2 more had repeated convulsions; all 6 have made an apparently satisfactory recovery."

"Nine of the 35 children had evidence of more prolonged intellectual and emotional difficulties, which in 6 seemed sufficiently severe and persistent to compromise their competitive status. . . . Two certainly were feebleminded. Three had mental irregularities of the sort often accompanying diffuse cortical damage. Of these, 1 also had epilepsy. One more child, though showing average intellectual ability, was an emotional cripple.

"Of these 6 children, 3 had obvious encephalopathy on admission to the hospital and in another 1 this complication developed in the hospital. In 2 cases, however, no suspicion of cerebral involvement was noted in the hospital.

"Three children, 1 of whom had mild cerebral symptoms and a high spinal fluid protein in the hospital, appeared to have suffered temporary developmental damage, from which recovery occurred after a period of years.

"No cases of asthma or bronchiectasis were discovered in the children studied, though these conditions were sought by history and physical examination and in a few cases by plain x-ray films of the chest."

A finding of 6 noncompetent persons out of 35 cases seemed to indicate that pertussis early in life must be considered an important threat to competence.

"Furthermore, though recovery to competitive level occurred after temporary developmental retardation, in 3 more cases it seemed entirely likely that these children's ultimate attainments had been somewhat compromised by the experience.

"Many of the children studied were exposed to known cases of whooping cough, and could probably have been protected by the use of hyperimmune serum."

Since pertussis vaccine seems prophylactically efficacious, the risks of its use in infancy are probably outweighed by those of the disease itself.

Tachycardia in Whooping Cough — FANCONI, G. AND FRISCHKNECHT, W.— *Helvetica paediatrica acta*, 5: 113 (May) 1950.

The authors were impressed by the occurrence of a prognostically favorable tachycardia in whooping cough outside the attacks; the literature on this subject is scanty. True myocardial involvement is considered rare in whooping cough but dilatation of the right ventricle, persistent between attacks, has been mentioned as a complication. Paroxysmal tachycardia has been observed in whooping cough.

The case reported was of a girl aged 8, with whooping cough, who was admitted with the suspicion of myocarditis because of increasing tachycardia and attacks of cyanosis on slightest effort. The whooping cough attacks had started 11 days before admission; 3 days before admission the girl developed a drug rash, and since then she had a tachycardia up to 160 per minute at rest. Sitting up or excitation resulted in cyanosis. The temperature ranged around 38° C. On admission the girl was asthenic and showed impairment of her general condition. Not more than 10 whooping cough attacks per day were observed. Cyanosis occurred on excitation or slight effort. The

chest plate showed a striate paracardial shadow, and numerous moist and dry rales were audible. In spite of streptomycin and penicillin treatment an interlobar effusion formed on the right side after two weeks. The girl had experienced hilar tuberculosis at the age of 3, but the subsequent favorable course of the effusion spoke against reactivation of the tuberculosis. The heart showed a normal shape; the blood pressure was 105/70 mm. but could not be determined in the standing position because of the danger of collapse. The pulse rate was at first around 160, and then remained at 130 to 140 for a week, while the temperature was subfebrile. Gradually the pulse rate became normalized at 100 after another week. There was no edema of hepatic stasis at any time. The electrocardiogram taken on admission showed a slightly negative T wave in the third lead, a right-sided type, and a sinus frequency of 160; three weeks later the T wave in the third lead was positive in spite of levorotation of the electric axis of the heart, and a sinus frequency of 107. The cyanosis subsided after four days. Intense red dermographism persisted and there was tremor of the fingers, and mechanical hyperexcitability of the nerve trunks without electric or chemical signs of spasmophilia; hyperthyroidism was absent. The blood picture showed 5.4 million erythrocytes, 103 per cent hemoglobin and 40,000 leukocytes with 1 per cent mature myelocytes, 2 per cent metamyelocytes, 6.5 per cent staff cells, 47.5 per cent segmented cells, 0.5 per cent eosinophils, 0.5 per cent basophils, 2.0 per cent monocytes, 39.5 per cent lymphocytes and 0.5 per cent plasma cells. Spinal fluid and blood sedimentation rate were normal. After four weeks the whooping cough subsided. The girl was discharged in good condition.

Obviously in this asthenic girl the vegetative nervous system had been sensitized by the preceding mumps, tonsillitis and grippe to such an extent that the whooping cough elicited a severe vegetative dystonia with tachycardia. The inner layers of the ventricular myocardium were relatively poorly supplied with oxygen due to the uneconomic cardiac work, resulting in a transitory negative T wave.

Among 200 unselected cases of whooping cough only 6 children showed a similar discrepancy between temperature and pulse curve in the sense of a tachycardia without any other cardiac symptoms; the cerebral component was striking in these children, including findings of apathy and increased glucose concentration of the cerebrospinal fluid, loss of consciousness after attacks, initial cerebral convulsions with apnea, and terminal cerebral convulsions with anatomic finding of cerebral edema, perivascular cells with fatty granules, cardiac dilatation and very slight fatty degeneration of the myocardium. In the last 2 cases the sinus tachycardia proved refractory to the sympathicolytic drug "Hydergin-Sandoz," while the remaining 4 cases were not studied in this respect. However, in 6 out of 20 other children with whooping cough abnormally shallow T waves were found electrocardiographically and were transitorily normalized by this drug in a dosage of 0.01 mg. per Kg. subcutaneously, with a reduction of the sinus frequency from 134 to 110 on the average. After cure of the whooping cough the electrocardiogram rapidly became normal.

The authors conclude that during the active stage of whooping cough the myocardial metabolism is relatively frequently disturbed by neurogenic sympathicotonic or humoral-adrenergic stimuli (about 30 per cent of their cases) while the sinus node seems much more rarely impaired by infectious-toxic or hormonal stimuli, acting directly or by way of the vegetative nervous system (about 3 per cent of their cases). Similar conditions seem to obtain in acute poliomyelitis.

Many signs of whooping cough can be reproduced experimentally in cats by electric stimulation of the hypothalamus; stimulation of the dynamogenic area which courses from the diencephalon to the hypothalamus leads to discharge of adrenalin and this permits the conclusion that the sympathicotonic electrocardiographic alterations in whooping cough may be the expression of central regulatory disturbances in the area of the hypothalamus.

According to the authors' observations, tachycardia in whooping cough seems more frequently caused cerebrally than cardially. Among 220 children with whooping

cough they encountered only 1 case of tachycardia with circulatory decompensation. This case involved a girl aged 3, with a birth weight of 2,000 Gm. and with slightly retarded development but without any history of disease. The whooping cough started with intense mucous secretion, vomiting and attacks of suffocation. For three days the temperature reached 39° C., and subsequently ankle edema supervened while the fever subsided. The girl was sent to the hospital, nephritis being suspected. Examination revealed tense edema of the legs and the dorsum of both feet but no edema elsewhere. The liver was palpable 1 fingerbreadth below the costal margin. The urine showed urobilinogenuria. The chest plate showed a few basal shadows, and auscultation revealed numerous moist consonant rales. Respiration was rapid; the cheeks were pink and there was no cyanosis. The pulse rate was 180; there was no definite cardiac enlargement. About 10 typical attacks occurred daily. The blood picture showed 111,000 leukocytes, with 0.5 per cent half mature myelocytes, 1 per cent metamyelocytes, 3 per cent staff cells, 28 per cent segmented cells, 2 per cent eosinophils, 5 per cent monocytes and 60.5 per cent lymphocytes. The red blood picture was normal and spleen and lymph glands were not enlarged.

Treatment included streptomycin, penicillin, "elkosin," digitalis, coramine and veritol. On admission, two weeks after onset of the whooping cough, the electrocardiogram showed a sinus frequency of 166, a flattened T wave in the first and second leads with a left-sided type and a biphasic T wave in the V_4 lead. After 10 days the edema increased, and face and thighs were involved. Nonprotein nitrogen and other blood chemistry were normal; there was only transitory slight albuminuria without casts or erythrocytes. The electrocardiogram showed low voltage. There were no pericardial friction rubs and roentgenologically no signs of pericardial or pleural effusion were demonstrable. Six days later the edema definitely decreased, and after another nine days it disappeared completely. The lungs were clinically normal at this time, but roentgenologically the markings were still increased paracardially on both sides. The blood picture showed 13,000 leukocytes with 61 per cent lymphocytes. Five days later the electrocardiogram was normal except for one ventricular extrasystole with compensatory interval. Four to five coughing spells still occurred each day. After six weeks the child was discharged; there was still slight cardiac enlargement. Thus a severe whooping cough with bronchiolitis was sufficient in this case to cause decompensation of the systemic and pulmonary circulation for three weeks. The sinus tachycardia in this case obviously was of a compensatory nature, on the basis of the Bainbridge reflex.

Circulatory decompensation in whooping cough may take place without sinus tachycardia; an illustrative case concerned a girl aged 9, who, when admitted three weeks after onset of her whooping cough and pneumonia, had facial cyanosis, intense hepatomegaly and meteorism. The electrocardiogram showed myocardial damage and a sinus frequency of 113. Nine days later the electrocardiogram was normal, with a sinus frequency of 100; the liver still extended to 2 fingerbreadths below the costal margin, cyanosis and meteorism had subsided, and the paracardial infiltrations had regressed. Three weeks later the liver was normal in size, the pneumonia was healed and the child was discharged. She still had 7 to 13 attacks daily. The heart was always of normal size. The pulse rate had ranged between 80 and 115, even with a rectal temperature of 38.5° C.

Symposium Section

Anorexia in Early Life

From time to time we read articles on subjects which we think are expressed so much better than we can present them that we feel they should be reprinted in full and not abstracted. Consequently, this section cannot be used to greater advantage than to give wider circulation to such articles which are so important in meeting these daily problems of practitioners. We have headed this with the title of anorexia in early life because down through the years we have listened attentively and otherwise to many papers intended to acquaint us with a way, purported to be the best, to overcome this cause of unhappiness and occasionally considerable disorganization in the domestic relations in the home. We have heard of too much milk and too little spinach as an unequivocal reason; favorite prescriptions known to the old professors of materia medica as "stomachics" designed to restore and promote functional activity of the stomach; tonics, especially the bitter kind containing quinine, quassia or gentian, to stimulate the appetite and improve digestion; removal of the food to discipline the little demons, and, to cut this short, we have read in the newspapers that fathers have actually murdered their kids because they would not eat. Obviously we grew weary and tired.

Profiting by the failures of these and equally silly procedures, younger men have gone into a huddle and have emerged with, at least, a better approach to many commonplace problems which annoy physicians and parents. The cradles of the Pilgrims had already become antiques during the latter part of the "gay nineties" when Diamond Jim Brady and Lillian Russell dominated the "gay" life. Later they were sought to be used as wood boxes for the gas-logged firesides while the custom to let the baby cry itself to sleep was generally advocated in the "books" on which not a few "climbed" to pediatric pinnacles. Thus the show, which spinach stole for so long, went on and gradually described a circle and has returned to the starting point. We have been compelled to realize that "babies are human beings" largely as a result of the writings of the late Andy Aldrich, as he was known to his contemporaries, and Mrs. Aldrich. Babies are being cuddled and loved again and Brahms' Lullaby and Rock-a-Bye Baby are emerging from oblivion and having a renaissance.

The growth and development of babies, which have always been of interest, as well as the means of guiding both, are being developed more logically. We may recall that the growth of the human body has never been illustrated better than Stratz did it in 1904. Reference to Figure 1, which has been used frequently, will be of assistance in formulating impressions of the length of different portions of the body, as compared with the head at different stages of life. This figure is being reproduced here chiefly to call attention to the period through which the newborn baby passes from birth through the first few years of life when "growth in length continues—so that he changes almost overnight from chubby babyhood to the typical linear habitus of childhood; he's exchanging the 'baby fat' for muscle, trading tissue for tissue rather than adding to his total mass." It is somewhere in the middle of this stage that "Johnny" begins "picking at his food, spilling things, and taking longer than usual to eat;—turning up his nose at food he used to be crazy about." When this occurs "both parents, the only living grandmother, one maiden aunt in town for a short visit, the nursemaid and the cook" complicate the dilemma with "smoggy" suggestions which eventually force the bewildered mother to " 'the doc' —the big brute in a white coat" who so recently, Johnny remembers, filled his tender bottom with a series of hot shots.

The solution of the problem is usually quite simple if a physical examination re-

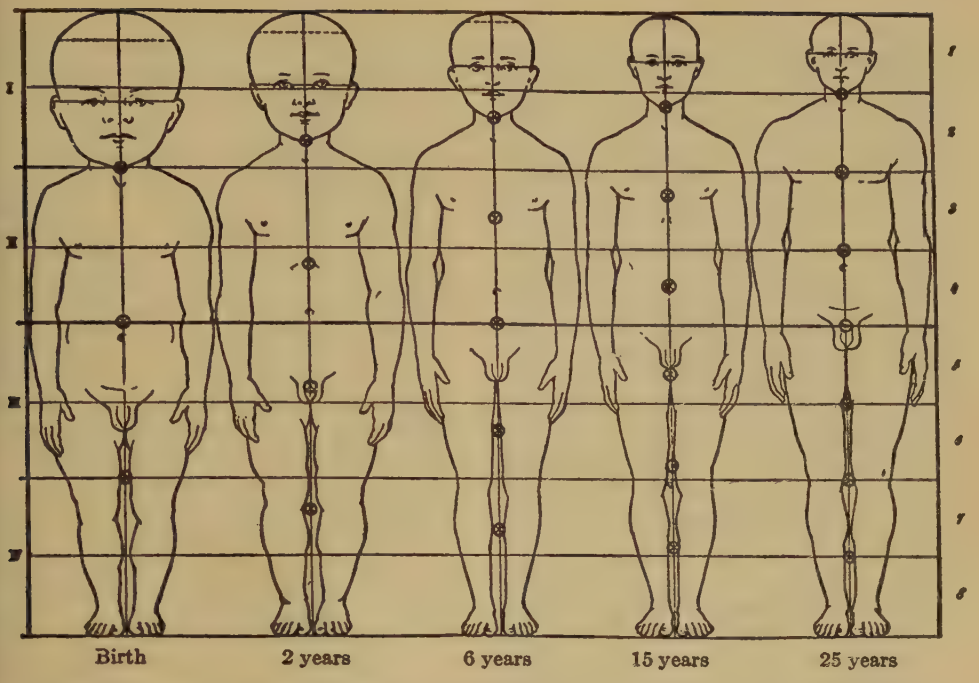


Fig. 1.—Growth proportions at different life periods, showing the length of different portions of the body as compared with the head. At birth the body is four heads high, while in the adult, it is eight heads high. (From Stratz, Der Korper des Kindes, 1904, 64, Fig. 42.)

veals that there is really nothing wrong, as it usually does. It depends, however, on the "doc" knowing the answer and on his ability to "sell" it to both parents—and all others concerned in the destiny of Johnny.

We have never read any article which gives this answer better or tells how it should be presented to parents than one which is titled, "JOHNNY WON'T EAT." This was written by Dr. Ralph V. Platou, who is Professor and Chairman of the Department of Pediatrics at Tulane University Medical School at New Orleans. This article is herewith reprinted in full as it appeared in the *Bulletin of the Tulane Medical Faculty* as one of a series of contributions in the Pediatric Departmental issue of May, 1950.

* * *

The busy physician probably meets no problem more annoying than that which faces him almost daily in the form of the cute, cheerful, apparently healthy 2 or 3 year old youngster who won't eat. The problem is important not only for its frequency and high nuisance value but also because its solution leaves the conscientious doctor with such a feeling of inadequacy. He is usually able to convince himself, after careful appraisal of the child, that there's nothing wrong but then has to face the far more difficult task of convincing the parents!

Let's review the story of a hypothetical case. Johnny, now about 20 months old and an only child, was the product of an uneventful pregnancy and a normal delivery; there were no neonatal difficulties, and he had been breast fed for six months. Weaning had been easily accomplished, vitamin supplements had been given early and adequately, solid foods had been introduced at the proper time, there had been no feeding difficulties, and his appetite had always been voracious. He weighed 15 pounds at 6 months, 23 at 1 year, and now weighs 30 pounds. Neuromuscular developmental performance always seemed in advance of average, dentition was normal, and there had been no illness except for two mild colds. The usual immunizations had been uneventfully completed at 11 months.

There was a family history of scattered, mild allergic manifestations, and one grandmother (who never saw this baby) died of tuberculosis. Both parents were healthy and of average stature.

About six weeks ago, the mother noticed that Johnny was "picking" at his food, spilling things, and taking longer than usual to eat; he was turning up his nose at food he used to be "crazy about." As a consequence, his temperature was recorded several times daily, and *he was weighed every day* for the next week. During these last six weeks, there had been no gain in weight, and, even more alarming, Johnny had lost 3 ounces!

Everything had been done. Both parents, the only living grandparent, one maiden aunt in town for a short visit, the nursemaid, and the cook had all offered suggestions. Father had his fill of eating spinach as an example; the ladies of the household had all coaxed, encouraged, and rewarded each mouthful Johnny saw fit to ingest. Everyone had assumed a stern expression, argued, threatened, and referred many times to starving children in less fortunate parts of the world. They even tried letting Johnny choose his own foods, and for one whole day they tried their best to pay no attention to him.

* * *

Finally, in desperation and in fear of an endless variety of serious diseases, Johnny was carried to your office—for a tonic. Since he remembered "the doc" most vividly as the big brute in a white coat who gave him all those painful "shots" just a few months previously, no one could blame the little guy for voicing violent objections to this trip and for making the examination as difficult as possible.

The examination revealed nothing of importance; urinalysis, blood counts, Mantoux test, sedimentation rate, and roentgenograms were normal. Johnny still wouldn't eat. A few scratch tests were applied for foods to which he most strenuously objected, but there were no positive reactions to explain his dislikes or his suspected allergic heritage.

* * *

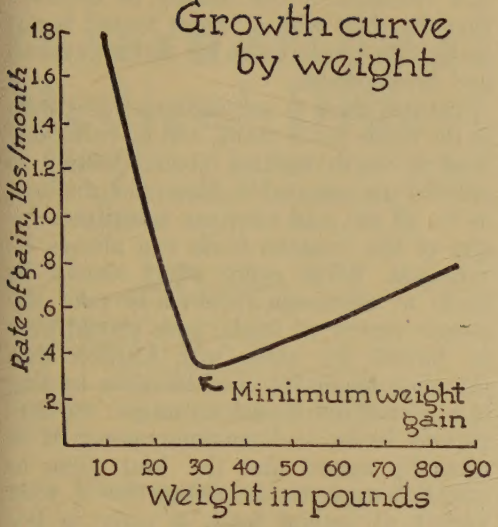
What's the reason for all this? Why should this period of minimal weight gain occur at this particular time? Quite satisfactory answers are apparent in normal growth and behavior patterns for this age. The rate of weight gain almost invariably decreases when children are about 1½ to 2 years of age or when they weigh about 30 pounds. An infant usually gains more than a pound each month for the first six months, less than a pound each month for the second six months, less than a half pound each month in the first part of the second year, and then he usually fails to show any appreciable gain at all, remaining at or about the same weight for weeks or months at a time. The accompanying charts† show this characteristic pattern. After a short period in the "valley of minimal weight gain," the curve resumes an encouraging upward trend.

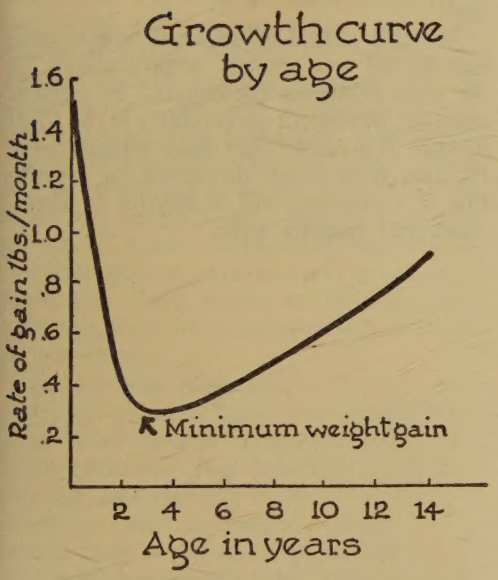
In the second place, Johnny is becoming extremely active. Having now developed great skill and speed in locomotion and finding innumerable new outlets for a seemingly inexhaustible store of energy and curiosity, he's really altogether too busy to take time out to eat. Growth in length continues, however, so that he changes almost overnight from chubby babyhood to the typical linear habitus of childhood; he's exchanging "baby fat" for muscle, trading tissue for tissue rather than adding to his total mass. It is surprising to most people to learn that a child's height at the second birthday is usually equal to about half his height at maturity.

Thirdly, anatomic growth of nervous tissue is about 60 per cent complete at the second birthday and then proceeds at a slower rate until it is practically complete 10 or 12 years later. Last but not least, the period of minimal weight gain coincides with that of psychologic negativism. Johnny's out to learn for himself and resents any efforts to confine his sphere of experimentation. All mothers recognize this "no-no" stage.

So Johnny is physiologic. Being also human, he appreciates attention and suddenly discovers that the very best time and place to get lots of attention is just at the time and place he's supposed to eat. Familiar to all parents is the resulting list of ingenious performances, ranging all the way from simple refusal of food to actually throwing it in his beseeching parent's face.

†Modified from Weinbach, A. B.: The Human Growth Curve, *Growth*, 5:217-255, 1941.





The picture has undoubtedly been overemphasized, though many parents would deny it. Many cases are milder, many more severe, but the essential pattern remains *monotonously similar*. The problem of minimal weight gain is of little or no concern in clinic practice or in large families but reaches its greatest proportions in small families of the well-to-do. Three factors are required to make the problem: physiologic and psychologic considerations *plus* overly conscientious parents. Many of the most typical examples are to be found in the doctor's own home!

* * *

What should the busy doctor do? Certainly a pat on the toddler's head and a "Don't worry, everything will be all right" to the parents is inadequate. First, he should emphasize that an appetite cannot be *bought*. The most carefully compounded prescription will not solve the problem; Johnny needs no medical measures. He isn't sick; he's only physiologic. In these times, when the gullible American public has such an unbounded faith in the magic powers of vitamins, we constantly hear demands for tonics or prescriptions to encourage an appetite. If *any* prescription is given at a time roughly coinciding with Johnny's natural resumption of gain, we have an immediate triumph, to be bandied about the bridge tables (or work benches) for months. But if the best possible tonic is given *before* Johnny is ready to resume gain, a dismal failure is likely to result. Unless definite medical indications are present, a tonic often serves only to aggravate the problem further by focusing even more unwarranted attention on it and leaving the impression that a true medical problem exists.

Second, he should explain that this phenomenal disturbing period of minimal weight gain, to which pediatricians facetiously refer as the "16-month disease," occurs almost regularly at about this age or weight. The doctor should anticipate the problem and explain to the parents when Johnny is about a year old that his present rate of weight gain obviously cannot continue forever. Thus forewarned, intelligent parents will avoid making a feeding problem mountain out of a physiologic molehill when Johnny exhibits this phenomenon. If the parents were not warned, however, and have already cooperated with Johnny in magnifying the situation, or if some recent common infection could conceivably be blamed, the doctor's ingenuity and oratorical ability will be taxed to convince them that no serious disease exists.

There are several simple specific instructions which usually prove helpful. The child should be required to relax, or at least quiet down, for 15 to 30 minutes before meals; it is unusual for a person of any age to relish a full meal at the height of vigorous exercise. Can you imagine a

steak dinner served between sets of tennis? Yet most parents expect their children to interrupt strenuous play, eat a satisfactory meal, and go right on without losing stride. (The cocktail hour is probably as effective for the relaxation it affords as for its alcoholic content.)

A second admonition, all too frequently neglected, is to omit any discussion of appetite, weight, or feeding difficulties in Johnny's presence. When his performance at meal time fails to elicit any reaction, the problem is well on the way to solution. Adequate usual helpings should be served at the usual hours, left for the usual time, and then removed with no comment or action, regardless of how much or how little has been taken. Any normal child will usually eat all he's going to eat in half an hour or less; longer meal times are usually manifest admissions of faulty technics.

Third, no foods should be allowed between meals; there is no virtue in confections taken between meals at any age, and in the young growing child they can serve only to replace foods much more valuable nutritionally. The amount of carbohydrate voluntarily taken by a child is probably directly related to the inadequacy of his diet in essential proteins, minerals, and vitamins. It can usually be assumed that the child with a "sweet tooth" is not getting the proper foods for optimal growth and development.

Fourth, there is no single essential item in the whole list of foods, and no particular food is worth fighting about. Johnny is entitled to reasonable likes and dislikes, as we all are, and adequate substitutes for any of the common foods can always be arranged. While every effort should be made to encourage children to take the largest variety of foods, none should ever be forced. We agree with Carlson that the most important considerations leading to a normal nutritional status are: variety, natural foods, and omnivorousness. It is generally agreed that the best time to establish appetites or likings for a wide variety of natural foods is early in life when such foods are introduced into the diet.

For this period of minimal weight gain and its all too obvious complications, as for most problems encountered in medical practice, intelligent prophylaxis is the ideal answer. It is hoped that these explanations, together with simple directions for prevention or correction, will be helpful to physicians and parents alike.

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Intravenous Iron in Anemia

It is not uncommon to see patients with microcytic hypochromic anemia who have had what would seem to have been adequate oral iron therapy for months and longer without benefit. Because of this, patients with this form of anemia without any demonstrable pathologic background who failed to respond to orally administered iron supplemented with vitamins, liver, etc. formerly remained in a state of chronic ill health or required transfusions. For this reason intravenous iron has been tried and there seems to be convincing evidence that it is occasionally dramatic in its effects.

It has been tried over a period of 20 years but the first impressive studies came from Wintrobe and his associates[1] in 1947. Using radio iron, they found that in anemic animals and patients most of the iron is removed from the plasma within a few hours. Some years ago Cappell had shown that the reticuloendothelial cells, by their metabolic activity, converted the finely particulate nature of iron into a soluble iron which was released into the blood plasma. This soluble iron is in a loose combination with the plasma proteins and is capable of passing through capillary walls to be stored in the lymphatic nodes and the parenchyma cells of the liver and kidney. Then Wintrobe and his associates showed that this soluble iron could be converted into hemoglobin, appearing as early as 48 hours after the administration of iron.

This has opened the way for clinical studies which have demonstrated the effectiveness of intravenous iron therapy in hypochromic anemia. One encouraging study comes from Denmark in which Gerbrandy[2] treated 9 patients with severe hypochromic anemia with intravenous injections of a soluble solution of saccharated oxide of iron. This preparation had an iron content of 2 per cent, and each injection provided 100 to 200 mg. of iron. The total dose of iron was 1,200 to 2,000 mg. The result was a rapid increase in the hemoglobin content of 1 to 4 per cent per day and the reticulocyte crises varied between 6 and 25 per cent. The blood volume increased simultaneously in 2 out of 3 patients. Thus the hemoglobin increase was even greater than indicated by the hemoglobin content. Thrombosis of injected veins, the development of painful infiltrations as the result of occasional extravasation into tissue surrounding the vein used, hemolysis and general vascular reactions after too rapid injections were undesirable complications, but Gerbrandy suggested that these could be largely prevented by slow injection and by employment of different veins for consecutive injections.

Another equally encouraging clinical report comes from Belfast, Eire, in which Ramsey[3] of the Royal Victoria and the Musgrave Park Emergency Hospital expresses the belief that intravenous iron therapy is now a practical method of treating microcytic hypochromic anemia and is the method of choice for patients unable to tolerate iron given orally or in those unable to absorb adequate quantities of iron. He used it in 11 cases in which his recordings and a chart seem to justify his

1. Greenberg, G. R., Ashenbrucker, H., Lauritsen, M. and Wintrobe, M. M.: The Anemia of Infection. IV. The Lack of Relationship Between the Diversion of Iron from the Plasma and the Origin of the Anemia, *J. Clin. Investigation*, **26:** 114 (January) 1947; Wintrobe, M. M., Greenberg, G. R., Humphreys, S. R., Ashenbrucker, H., Worth, W. and Kramer, R.: The Anemia of Infection. III. The Uptake of Radioactive Iron in Iron-Deficient and in Pyridoxine-Deficient Pigs Before and After Acute Inflammation, *J. Clin. Investigation*, **26:** 103 (January) 1947.

2. Gerbrandy, J.: Intravenous Iron Therapy in Hypochromic Anemia, *Nederl. tijdschr. v. geneesk.*, **93:** 4009 (November 26) 1949. Note. This was obtained as an abstract of current medical literature in *J.A.M.A.*, **143:** 505 (June 3) 1950.

3. Ramsey, A. S.: Intravenous Iron in the Treatment of Anaemia, *Brit. M.J.*, **1:** 1109 (May 13) 1950.

belief that the response was dramatic. He likewise used the saccharated oxide of iron. His procedure was to use 100 mg. daily for several doses and gradually increase to 200 mg. and even 300 mg. So his method differed little from the one used by Gerbrandy. He did observe that it was unfortunate that the total amount of iron required will not be tolerated by all patients without prohibitive toxic reactions if given in a single dose. So it would seem that further study will be necessary to determine the maximum single dose. Ramsey states that he tried the antihistaminic drugs in some patients without preventing or reducing the toxic reactions. However, he found that a full course always consists of fewer than 10 injections, and he seems convinced that it is the most convenient method of treating patients who are unable to tolerate oral preparations of iron.

Khellin in Anginal Pain

Khellin, the active principle of a plant known as *Ammi visnaga* grows wild in Arabia, Egypt and Eastern Mediterranean countries. Three crystalline compounds have been isolated from the fruit of the plant and one of them called visammin has been demonstrated to be capable of relaxing smooth muscle. This new substance is better known as khellin and has been found to be a powerful coronary vasodilator in animals, causing a definite increase in coronary blood flow without demonstrable ill effect on the myocardium.

It was used first in Egypt but more recently Rosenman and associates[1] report their results in 14 cases of angina pectoris, most of which have been observed for several years in the Cardiovascular Department of the Medical Research Institute of Michael Reese Hospital in Chicago. These patients with angina were treated with 100 to 200 mg. orally which was the amount given daily. This amount was given for from 3 to 13 weeks and in one instance as long as 40 weeks. Eight patients with chronic cor pulmonale showed distinct improvement in respiration, color, exercise capacity and dyspnea following this oral administration. Single intramuscular injections of 200 mg. of visammin resulted in significant improvement in 9 of 21 patients with acute bronchial asthma.

For the purpose of avoiding any error in judging the effects of this drug, Rosenman and associates administered it alternately with placebos. The effects when no drug was given were compared with those resulting from its administration. It was used on patients who had been under observation for several years, during which time the characteristics of their anginal syndrome had been well delineated. The frequency of anginal attacks in relation to the number of glyceryl trinitrate tablets taken was also given weight in determining the value of khellin. But the conclusions of these investigators was reached for the most part by the dramatic results obtained in the patients with unequivocal severe attacks of angina.

The beneficial action of visammin in some patients varied in degree. In a significant number, after oral administration, there was moderate to decided improvement but in most instances there seemed to be complete freedom from anginal pain, despite subsequent increase in activity. This was best seen in patients with severe angina who required a large number of glyceryl trinitrate tablets daily. Frequently, freedom from angina persisted for as long as two weeks after the drug had been stopped. On the other hand, some of the mild cases showed no improvement and others experienced relief while receiving the placebos.

In brief, these authors have concluded that visammin is a useful drug in angina pectoris, in chronic cor pulmonale and, to a lesser extent, in acute bronchial asthma. Similar impressions have been gained from another clinical study of a series of cases in England.[2] The drug is not without toxic effects so all authors believe that further study of the drug will be necessary to determine its clinical usefulness, its contraindications, its toxicity and the mechanism of its action.

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1. Rosenman, R. H., Fishman, A. P., Kaplan, S. R., Levin, H. G. and Katz, L. N.: Observations on the Clinical Use of Visammin (Khellin), *J.A.M.A.*, **143:** 160 (May 13) 1950.

2. Dewar, H. A. and Grimson, T. A.: Khellin in the Treatment of Angina of Effort, *Brit. Heart J.*, **12:** 54 (January) 1950.